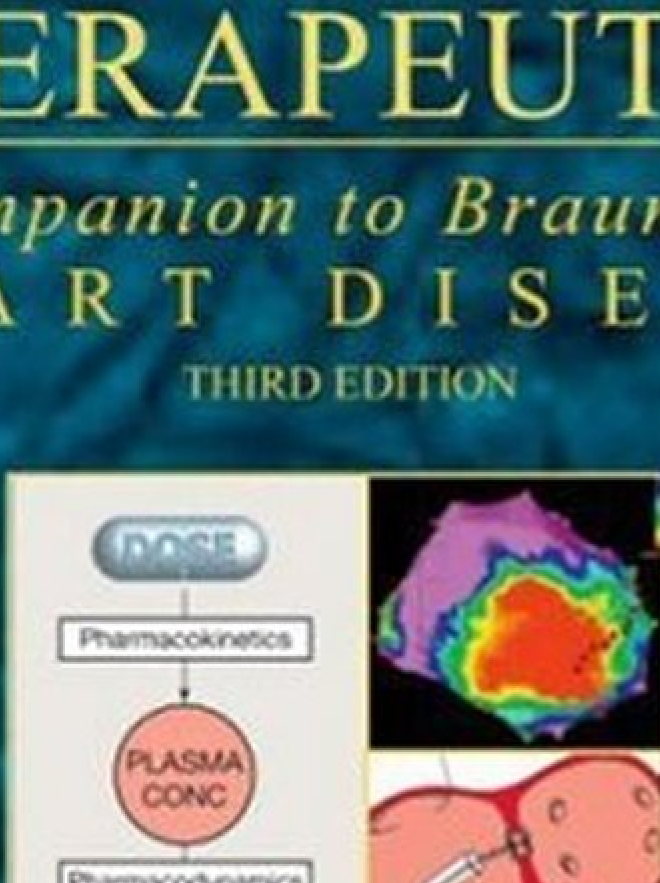
ANTMAN

CARDIOVASCULAR THERAPEUTICS

A Companion to Braunwald's HEART DISEASE

THIRD EDITION



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Foreword

As recently as four decades ago, the treatment options available for patients with cardiovascular disease were quite limited. The major therapeutic measures included bed rest and warfarin for acute myocardial infarction; nitroglycerin for angina pectoris; dietary sodium restriction, bed rest, digitalis, and mercurial or thiazide diuretics for heart failure; quinidine or procainamide for tachyarrhythmia; large, clumsy pacemakers for complete heart block; sodium restriction and sympathetic blocking agents for severe hypertension; and palliative surgery for a limited number of complex congenital cardiac malformations. Mild or even moderate hypertension was not treated, nor were effective agents available to lower serum cholesterol in patients with coronary artery disease and hypercholesterolemia. Percutaneous coronary revascularization, internal cardioverter-defibrillators, and modern pharmacotherapy of myocardial ischemia and fibrinolysis had not yet been developed. β-Adrenergic antagonists, angiotensin-converting enzyme inhibitors, and statins also were off in the future.

No aspect of medicine has undergone a more radical transformation in the past 40 years than has cardiovascular therapeutics, and the results have been truly spectacular. Overall mortality rates from heart disease have been declining steadily, and the age-adjusted mortality secondary to coronary artery disease, the most common cause of cardiovascular deaths, has been falling at almost 1% per year. Effective treatment—albeit not cure—of almost all forms of heart disease is now possible, allowing a majority of patients with cardiovascular disease to live longer lives of high quality.

Dr. Antman and his associate editors—Drs. de Lemos, Givertz, Josephson, Oparil, and Sacks—and a constellation of superb contributing authors should be congratulated on providing the most comprehensive modern text in cardiovascular therapeutics. Instead of focusing narrowly on a single therapeutic modality—drugs, interventional cardiology, devices, or surgery—this contemporary, authoritative, and eminently readable book deals with *total* patient management. The several types of therapy that can be offered for specific cardiovascular disorders are presented lucidly and in sufficient detail to serve as the basis for managing the vast majority of patients with cardiovascular disease. This excellent text will be of immense value not only to cardiologists but also to internists and primary care physicians, who are shouldering increasing responsibilities for the management of patients with cardiovascular disease.

This third edition of *Cardiovascular Therapeutics* is essentially a new book when compared with its predecessor. There are three new Section Editors (Drs. James de Lemos, Michael Givertz, and Frank Sacks) and many new contributors. Forty-two of the 55 chapters are new or radically revised. The three appendices, on cardiovascular drugs, pacemakers and implantable cardioverter-defibrillators, and circulatory support devices, will be extremely useful.

We are very proud that *Cardiovascular Therapeutics* is a companion to *Heart Disease: A Textbook of Cardiovascular Medicine*. We hope that the new edition, along with the other books now available as companion volumes to *Heart Disease*, will serve as an extensive cardiovascular information system.

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Preface

This third edition of *Cardiovascular Therapeutics*, a text originally proposed by the late Thomas Woodward Smith as a companion to *Heart Disease*, continues to emphasize an evidence-based approach to therapeutic recommendations for management of the patient with cardiovascular disease. I had the privilege of working with an experienced group of Section Editors—Dr. James de Lemos, Dr. Michael Givertz, Dr. Mark Josephson, Dr. Suzanne Oparil, and Dr. Frank Sacks—in the preparation of the new edition. The reader is provided with cutting-edge recommendations for treatment of common problems such as ischemic heart disease, heart failure, dyslipidemia, dysrhythmias, hypertension, congenital heart disease, pericardial disease, cardiovascular disorders during pregnancy, and infective endocarditis.

For this edition of *Cardiovascular Therapeutics*, 16 chapters are completely new, and 33 chapters and the 3 appendices have been radically revised. The introductory chapter on tools for understanding the evidence that drives guidelines recommendations has important new information from contemporary clinical trials. Critical chapters on emerging therapeutics approaches such as gene therapy and stem cell therapy and the biology and clinical trial results with drug-eluting stents have been added. To assist the clinician in understanding the details of the development and approval of cardiovascular devices, representatives from the U.S. Food and Drug Administration have contributed a new chapter. Appendix 1, on cardiovascular drugs, has been updated to reflect the additions to the pharmacotherapeutic armamentarium. Appendix 2 presents invaluable tables, algorithms, and figures to guide the clinician through the process of selecting and monitoring devices for treating dysrhythmias. Appendix 3 has the latest information on intracorporeal and extracorporeal circulatory support devices.

Primary care physicians and cardiologists from across a range of training and experience will find this new edition of the book a critical resource for their practice. Once again, there are extensive cross-references to the seventh edition of *Heart Disease* (designated HD7e in this textbook), edited by Douglas Zipes, Peter Libby, Robert Bonow, and Eugene Braunwald. By using *Cardiovascular Therapeutics* along with HD7e and the other books in the companion series in a synergistic fashion, clinicians will be able to make the most of an extraordinarily rich set of resources that have been rigorously prepared.

Acknowledgments

A new edition of a text such as *Cardiovascular Therapeutics* provides an opportunity to acknowledge the contributions of many individuals. The continued training in rigorous scientific thinking and clinical medicine provided by Eugene Braunwald is a treasured experience for which I am extremely grateful. The scientific and personal collaborations with Joseph Loscalzo have been an important asset in framing my thinking in preparing this edition. I wish also to acknowledge the generations of Cardiovascular Division Fellows and extraordinary faculty at the Brigham and Women's Hospital, under the leadership of Peter Libby, who provided the inspiration and professional environment for my work on *Cardiovascular Therapeutics*. A special note of gratitude is due to my colleagues in the TIMI Study Group, many of whom have contributed both directly and indirectly to this text. Sylvia Judd, my administrative assistant, continues to be an invaluable resource in countless ways related to the preparation and production of this book.

Finally, on behalf of all of the Section Editors and contributors, I wish to express appreciation for the efforts of the team at Elsevier who worked diligently to publish this text.

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SECTION 1

Decision-Making and Therapeutic Strategies in Cardiovascular Medicine

Chapter 1

Tools for Assessment of Cardiovascular Tests and Therapies

Elliott M. Antman, Robert M. Califf, and Joel Kupersmith

CHAPTER CONTENTS

Therapeutic decision-making in cardiovascular medicine should proceed through an orderly sequence of events beginning with elicitation of the pertinent medical history and performance of a physical examination (see Chapters 7 and 8 of *Heart Disease*, 7th ed.). In the ideal situation, a variety of diagnostic tests are ordered and the results are integrated into an assessment of the probability of a particular cardiac disease state. Based on this information and an assessment of the evidence to support various treatments, a therapeutic strategy is formulated. The purpose of this chapter is to provide an overview of the quantitative tools used to interpret diagnostic tests, evaluate clinical trials, and select a treatment plan. The principles and techniques discussed serve as a foundation for placing the remainder of *Cardiovascular Therapeutics* in perspective and serve as the foundation for the generation of guidelines for clinical practice.[1] Appropriate application of the therapeutic decision-making tools that are described and adherence to the guideline documents based on the tools translate into improved patient outcomes—an area where cardiovascular specialists have distinguished themselves among the various medical specialties.[2-5]

INTERPRETATION OF DIAGNOSTIC TESTS

A useful starting point for interpreting a diagnostic test is the standard 2 × 2 table describing the presence or absence of disease (as determined by a gold standard) and the results of the test.[6] Even before the results of the test are known, clinicians should estimate the pretest likelihood of disease based on its prevalence in a population of patients with clinical characteristics similar to the patient being evaluated. Because no diagnostic test is perfect, a variety of statistical terms are used to describe its operating characteristics (Fig. 1–1). *Sensitivity* is the proportion of patients with the disease who have a positive test. *Specificity* is the proportion of patients without the disease who have a negative test. The probability that a test will be negative in the presence of disease is the *false-negative rate,* and the probability that a test will be positive in the absence of disease is the *false-positive rate.* Other useful terms are *positive predictive value,* which describes the probability that the disease is present if the test is positive, and *negative predictive value,* which describes the probability that the disease is absent if the test is negative. The STARD (Standards for Reporting of Diagnostic Accuracy) initiative sets forth guidelines on how studies of reports on diagnostic accuracy should be prepared.[7]

Because the results of diagnostic tests are dependent on the profiles of patients being studied, the *likelihood ratio* has been introduced to express how many times more (or less) likely a test result is to be found in patients with disease compared with those without disease (see Fig. 1–1).[8] (This is analogous to Bayes' rule, in which one updates the prior probability of a disease state based on the conditional probability of the observed test result to form a revised or post-test probability of a disease state). By multiplying the pretest odds of disease by the likelihood ratio, clinicians can establish a post-test likelihood of disease and determine whether that likelihood

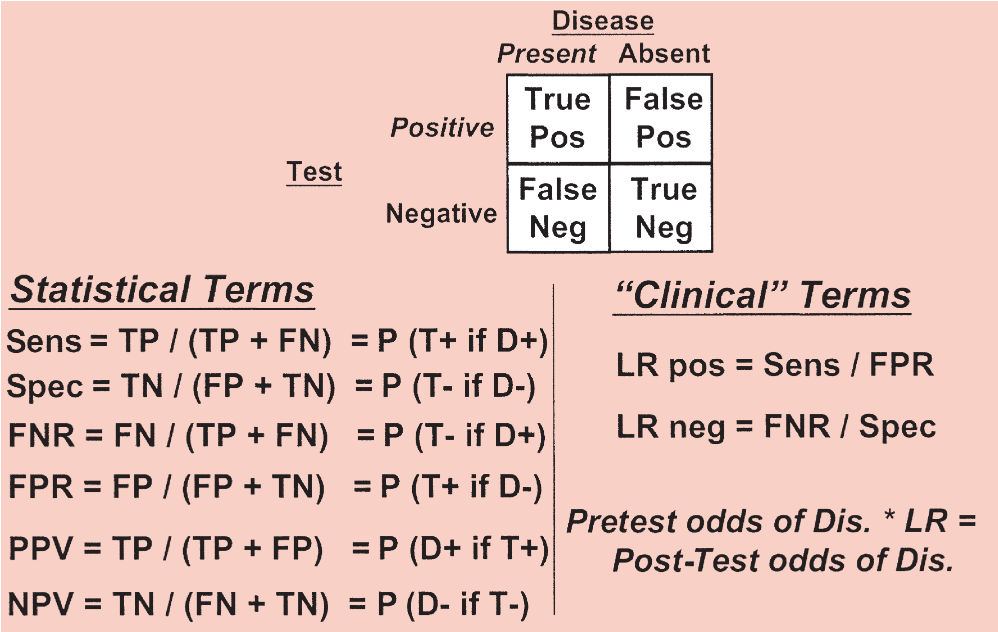


Figure 1–1 Interpretation of diagnostic tests. The standard 2 × 2 table (*top*) assigns patients into one of four cells based on the presence or absence of disease (according to a gold standard) and the results of a diagnostic test (positive or negative). Seven commonly used statistical terms that describe the operating characteristics of the test are given (*bottom left*). A clinically useful term is *likelihood ratio,* which expresses how many times a test result is more or less likely to be found in patients with disease compared with those without disease. This enables clinicians to update their pretest estimate of the odds of disease (Dis) and formulate a post-test odds of disease. The statistical terms can be interpreted along the lines of the following example: Sensitivity = probability (P) that the test is positive (T+) if the disease is present (D+). False Neg (FN), false negative; False Pos (FP), false positive; FNR, false-negative rate; FPR, false-positive rate; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; True Neg (TN), true negative; True Pos (TP) true positive.

crosses the threshold for treatment.[9] For example, in a patient with chest discomfort, the presence of ST-segment elevation on the 12-lead ECG (diagnostic test) not only increases the probability that myocardial infarction (MI [disease state]) is present but also moves the decision-making process to the treatment threshold for reperfusion therapy without the necessity for further diagnostic testing. In the same patient, a nondiagnostic electrocardiogram does not appreciably alter the post-test likelihood of an MI. Additional testing (e.g., biomarkers of cardiac damage) is needed to establish the diagnosis of MI.

The example shown in Figure 1–1 is for a diagnostic test that produces dichotomous results—either positive or negative. Many tests in cardiology provide results on a continuous scale. Typically, diagnostic cutoffs are established based on tradeoffs between sensitivity and specificity. In the example shown in Figure 1–2, a diagnostic cutoff in the region of point A would have high sensitivity because it identifies the majority of patients with disease (true-positive results), but it does so at the expense of reduced specificity because it falsely declares the test to be abnormal in patients without disease. Using a range of diagnostic cutoffs for a positive test (e.g., see Fig. 1–2A to C), a receiver operating characteristic (ROC) curve can be plotted to illustrate the relation between sensitivity and (1-specificity).[9] Better tests are those in which the ROC curve is positioned close to the top left corner. Comparison between two tests over a range of diagnostic cutoffs is accomplished by calculating the area under the ROC curve; the test with the larger area is considered superior.[9] In practice, it is difficult for many clinicians to apply the quantitative concepts illustrated in Figure 1–2 at the bedside. This has led many laboratories to provide annotated reports to assist practitioners in forming a probabilistic estimate of the likelihood of a disease state being present.

CLINICAL TRIALS

Need for Clinical Trials

Therapeutic recommendations for various cardiovascular diseases discussed in this text have been formulated after intensive clinical investigation. Uncontrolled observational studies of populations provide valuable insight into pathophysiology and serve as the source for important hypotheses regarding the potential value of particular interventions. However, it is a rare therapy in medicine that has the dramatic effectiveness of penicillin for pneumococcal pneumonia so that epidemiologic data alone are sufficient for scientific acceptance and adoption into clinical practice. In view of the variability of the natural history of cardiovascular illnesses and the wide range of individual responses to interventions, clinical investigators, representatives of regulatory agencies, and practicing physicians have come to recognize the value of

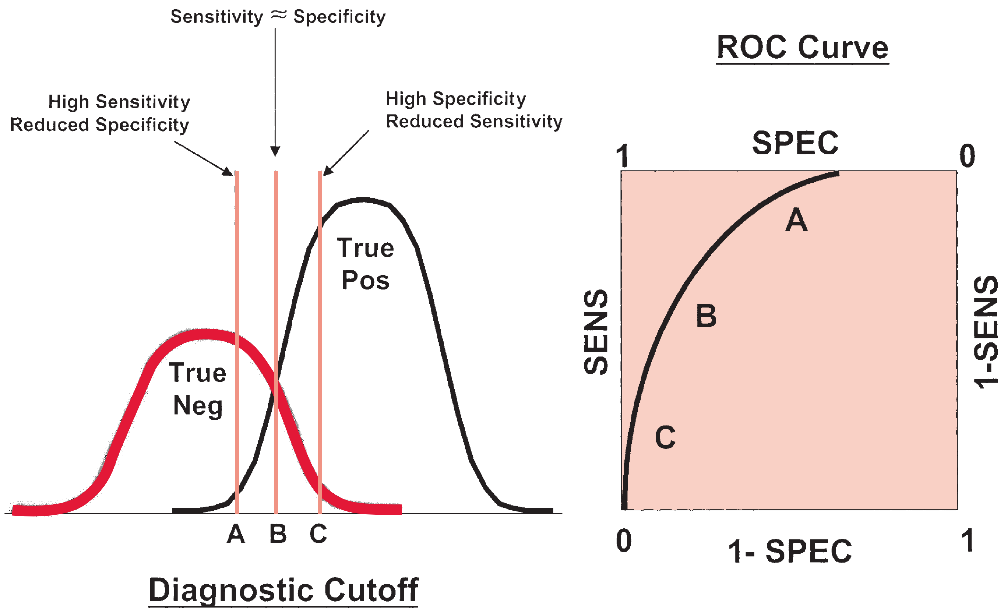


Figure 1–2 Influence of diagnostic cutoffs on interpretation of test performance. *Left*, Distributions of patients for whom the disease is present (True Pos) and the disease is absent (True Neg). Three different levels of a diagnostic cutoff (A to C) are shown for a test that is reported on a continuous scale. Diagnostic cutoff A has high sensitivity (identifies the majority of true-positive patients), although it does so at the expense of reduced specificity (a large number of true-negative patients are classified as having disease). At the other extreme, diagnostic cutoff C has high specificity (few true-negative patients classified as having disease) but at the expense of reduced specificity (a large proportion of true-positive patients are not classified as having disease). *Right*, Typical receiver operator characteristic (ROC) curve, illustrating the impact of cutoff levels A to C with respect to sensitivity (SENS) and specificity (SPEC).

Table 1–1 Phases of Evaluation of New Therapies

Phase	Features	Purpose
I	First administration of a new therapy to patients	Exploratory clinical research to determine if further investigation is appropriate.
II	Early trials of new therapy in patients	Designed to acquire information on dose-response relationship, estimate incidence of adverse reactions, and provide additional insight into pathophysiology of disease and potential impact of new therapy.
III	Large-scale comparative trial of new therapy versus standard of practice	Definitive evaluation of new therapy to determine if it should replace current standard of practice. Randomized controlled trials required by regulatory agencies for registration of new therapeutic modalities.
IV	Monitoring of use of therapy in clinical practice	Post "marketing" surveillance to gather additional information on impact of new therapy on treatment of disease. Rate of use of new therapy and more robust estimate of incidence of adverse reactions established from registries.

a control group and a rigorously performed clinical trial before widespread acceptance of a treatment.[10] The sequence of phases for the evaluation of new therapies is seen in Table 1–1.

Cardiovascular medicine has made a transition from practice based in large part on nonquantitative pathophysiological reasoning to practice oriented around "evidence-based medicine."[1] The importance of this concept has been reinforced by demonstration in clinical trials that widely accepted concepts have been associated with a substantial adverse effect on mortality rates. Type I antiarrhythmic drugs were often prescribed because of frequent premature beats until the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that such treatment increased the risk of death.[11] Despite the recognized importance of empirical evidence in guiding therapeutic decision-making, only with the advent of powerful computers have computational and organizational capabilities begun to meet researchers' needs.

Despite current limitations, evidence-based therapeutic recommendations that involve drugs, devices, and procedures

are in demand, with managed care, cost-saving measures, and guidelines published by authoritative groups playing increasingly prominent roles in the fabric of clinical medicine.[12] With the increasing number of elderly patients in the population, there also is a clear need for improved information on their response to therapeutic interventions.[13] Thus, the proper design, conduct, analysis, interpretation, and presentation of a clinical trial form an “indispensable ordeal” for investigators.[14,15] Over the last several years, a number of scandals related to clinical trials have occurred, leading to public distrust of the clinical trial process.[16,17] One solution that has been put in place is a mandate that clinical trials be registered in a public domain-accessible website; examples of a clinical trial registration data set have also been published.[18,19] Practitioners must also acquire the tools to critically read reports of clinical trials and, when appropriate, to translate the findings into clinical practice without the lengthy delays that occurred in the past. This is an especially important task for generalist physicians because of the increased emphasis on primary care physicians to control health care costs by managing chronic disease with appropriate testing and referral. In addition, there is evidence that generalist physicians are less aware, or less certain of the results, of clinical trials than are specialists.[20]

The sheer volume and broad range of clinical trials in cardiology are too large for even the most conscientious individual to digest on a regular basis. This has stimulated increased interest in biostatistical techniques to combine the findings from randomized controlled trials (RCTs) of the same intervention into a meta-analysis or an overview.[21]

Clinical Trial Design

Because of the importance of clinical trial findings, it is essential that investigators thoughtfully formulate the scientific question to be answered and have realistic estimates of the sample size required to show the expected difference in treatments. Trials that conclude there is no statistically significant difference between treatment A and treatment B are often undersized and lack sufficient power to detect a difference when one truly exists. A well-coordinated organizational structure, consisting of experienced trialists, biostatisticians, and data analysts, is important to prevent such pitfalls in trial design such as unrealistic assessments of the ease of patient recruitment and timetable for completion of the trial.

The stages of a clinical trial are summarized in Table 1–2. These should be viewed as a rough guide to the orderly sequence of events that characterizes the clinical trial process. The dividing lines between stages are often indistinct. For example, sites at which patients are randomized may be brought into the trial in a rolling fashion so that some of the features of the protocol–development stage may overlap with the patient–recruitment phase. It is possible that some of the

Table 1–2 Stages of a Clinical Trial

Stage	Activities During Stage	Event Marking End of Stage
Initial design	Formulation of scientific question, outcome measures established, sample size calculated	Initiation of funding
Protocol development	Trial protocol and manual of operations written, case report forms developed, data management systems and monitoring procedures established, training of clinical sites completed	Initiation of patient recruitment
Patient recruitment	Channels for patient referrals established, development of regular monitoring procedures of trial data for accuracy, patient eligibility, and site performance; preparation of periodic reports to DSMB for review of adverse or beneficial treatment effects	Completion of patient recruitment
Treatment and follow-up	Continued monitoring of patient recruitment, adverse effects and site performance; updated trial materials sent to enrolling sites; reports sent to DSMB and recommendations reviewed; adverse event reports filed with regulatory agency; timetable for trial close-out procedures established	Initiation of close-out procedures
Patient/trial close-out	Identification of final data items that require clarification so data base can be “cleaned and locked”; initiation of procedures for unblinding of treatment assignment, termination of study therapy, and monitoring of adverse events following discontinuation of treatment; preparation of final reports to DSMB; preparation of draft of final trial report	Completion of close-out procedures
Termination	Verify that all sites have completed close-out procedures including disposal of unused study drugs; review final trial findings and submit manuscript for publication; submit final report to regulatory agency.	Termination of funding for original trial
Post-trial follow-up (optional)	Recontact enrolling sites to acquire long-term follow-up on patients in trial; link follow-up data with initial trial data and prepare manuscript summarizing results.	Termination of all follow-up

Adapted from material in Meinert C: Clinical Trials. Design, conduct, and analysis. New York, Oxford University Press, 1986.
DSMB, data safety monitoring board.

early sites that enroll patients gain sufficient experience with the protocol to achieve different results than those of the sites that join the trial later. Evidence of this phenomenon is typically sought by performing a test for interaction between the enrolling site and treatment effect when the data are analyzed. The situation can rapidly become quite complex when international differences in treatment effect are observed—especially if benefit is noted predominantly in one international region and not in others.[22] Of note, even after a fully executed development sequence from phase I through phase III trials, important adverse consequences of a new treatment may not be apparent. Although post-marketing (phase IV) trials (see Table 1–1) are theoretically supposed to catch such problems and identify treatments that should be withdrawn from clinical use, such trials are rarely conducted and several authorities have called for renovation of the drug regulation process to protect the population from harmful therapies.[23]

The term *control group* refers to those subjects in a clinical trial who receive the treatment against which the test intervention is being compared. Requirements for the control and test treatments are outlined in Table 1–3. *Randomized controlled trials* typically incorporate both test and control treatments and are considered the gold standard for the evaluation of new therapies. However, the previously noted definition of a control does not require that the treatment be a placebo, although frequently this is the case, because new treatments may have to be compared with the current standard of practice to determine whether they are more efficacious (e.g., new antithrombin agents versus unfractionated heparin; see Chapters 5 and 10) or within a range of effectiveness deemed to be clinically not inferior (e.g., bolus thrombolytic versus accelerated infusion regimen of alteplase; see Chapters 5 and 11).[6] This definition does not require that the control group be a collection of subjects distinct from the treatment group studied contemporaneously and allocated by random assignment. Other possibilities include nonrandomized concurrent and historical controls, crossover designs and withdrawal trials, with each patient serving as a member of both the treatment and control groups, and group or cluster allocations, in which groups of subjects or a treatment site is assigned as a block to either test or control.[6]

Table 1–3 Requirements for the Test and Control Treatments

They must be distinguishable from one another.
They must be medically justifiable.
There must be an ethical base for use of either treatment.
Use of the treatments must be compatible with the health care needs of study patients.
Either treatment must be acceptable to study patients and to physicians administering them.
There must be a reasonable doubt regarding the efficacy of the test treatment.
There should be reason to believe that the benefits will outweigh the risks of treatment.
The method of treatment administration must be compatible with the design needs of the trial (e.g., method of administration must be the same for all the treatments in a double-blind trial) and should be as similar to real-world as practicable.

Reproduced from Meinert C. Clinical Trials. Design, conduct, and analysis. New York, Oxford University Press, 1986, p 469.

Two broad types of controlled trials exist: the *fixed sample size design*, in which the investigator specifies the necessary sample size before patient recruitment, and the *open or closed sequential design*, in which sequential pairs of patients are enrolled (one to test and one to control) only if the cumulative test-control difference from previous pairs of patients remains within prespecified boundaries.[14] The sequential trial design is usually less efficient than the fixed sample size design and is practical only in situations in which the outcome of interest can be determined soon after enrollment. In addition, trials with the fixed design can be organized in a manner in which randomization and/or follow-up continues until the requisite number of endpoints is reached, thus ensuring that inadequate numbers of endpoints will not hamper the trial interpretation.

Case-control studies that involve a comparison of persons with a disease or outcome of interest (*cases*) with a suitable group of subjects without the disease or outcome (*matched controls*) are integral to epidemiologic research, are not strictly clinical trials, and are not discussed in this chapter.[24]

Randomized Controlled Trials

The RCT is the standard against which all other designs are compared for several reasons.[15] In addition to the advantage of incorporating a control group, this type of trial centers around the process of randomization, which has the following three important influences:

1. It reduces the likelihood of patient selection bias in allocation of treatment that may occur either consciously or unconsciously.
2. It enhances the likelihood that differences between groups are random so that comparable groups of subjects are compared, especially if the sample size is sufficiently large.
3. It validates the use of common statistical tests such as the χ^2 test for a comparison of proportions and Student's *t* test for a comparison of means.[9]

Randomization may be fixed over the course of the trial or may be adaptive based on the distribution of prior randomization assignments, baseline characteristic frequencies, or observed outcomes.[25] Fixed randomization schemes are more common and are specified further according to the allocation ratio (uniform or nonuniform assignment to study groups), stratification levels, and block size (i.e., constraining the randomization of patients to ensure a balanced number of assignments to the study groups, especially if stratification is used in the trial). Ethical considerations related to randomization have been the subject of considerable discussion in clinical trial literature.[26,27]

Clinicians usually participate in an RCT if they feel sufficiently uncertain about the potential advantages of the test treatment and can confidently convey this uncertainty to the patient, who must provide informed consent.[28] It is important that clinicians realize that in the absence of rigorously obtained data, many therapeutic decisions believed to be in the best interest of the patient may be ineffective or even harmful. To identify the appropriate therapeutic strategies from a societal perspective, RCTs are needed.

A difficult philosophical dilemma arises when one considers that as patients are enrolled in a trial, evidence is

accumulating that tends to favor one study group over the other, and the degree of uncertainty about the likelihood of benefit or harm is constantly being updated. Because clinicians may feel uneasy about enrolling a patient who may be randomized to a treatment that the accumulating data suggest might be inferior but has not yet been proved statistically to be so with a conventional level of significance, the outcome data from the trial are not revealed to the investigators during the patient recruitment stage. The responsibility of safeguarding the welfare of patients enrolled in the trial rests with an external monitoring team referred to as a *Data Safety Monitoring Board* (DSMB) or *Data Safety Monitoring Committee* (DSMC).[27,29-32] Several prominent examples of the early termination of large RCTs because of compelling evidence of benefit or harm from one of the treatments under investigation are evidence that the DSMB has become an integral element of clinical trial research.[33]

When both the patient and the investigator are aware of the treatment assignment, the trial is said to be *unblinded*. Trials of this nature have the potential for bias, particularly during the process of data collection and patient assessment, if subjective measures such as the presence or absence of congestive heart failure are tabulated.[27] In an effort to reduce bias, progressively stricter degrees of blinding may be introduced. Single-blind trials mask the treatment from the patient but permit it to be known by the investigator; double-blind trials mask the treatment assignment from both the patient and investigator; and triple-blind trials also mask the actual treatment assignment from the DSMB and provide data only in the form of group A and group B.

The specialty of cardiology is replete with examples of RCTs. An area particularly rich in this regard is the study of treatments for ST-elevation MI (see Chapter 11), in which several types of RCTs have been performed. These trials have been broadly classified into minitrials and megatrials. A further subdivision of the minitrials includes those that are of limited sample size and focus almost exclusively on mechanistic data and those with a sample size an order of magnitude larger and hybrid goals focusing on mechanistic data as they relate to mortality. Because of the practical limitations of the very large sample size required when mortality is used as the primary endpoint in trials of new cardiovascular therapies, the majority of which are expected to have a treatment effect of 15% to 20%, interest has arisen in the use of composite endpoints such as the sum of death, nonfatal recurrent MI, and recurrent ischemia as the primary endpoint.[34] Trials that use composite endpoints, especially those that involve sophisticated biological measurements (e.g., ejection fraction ascertained by radionuclide ventriculography), are more likely to have missing data than are those that use mortality as the primary endpoint. This ascertainment bias or noninformative censoring of the data may necessitate statistical adjustments to compensate for missing data.[35]

Nonrandomized Concurrent Control Studies

Trials in which the investigator selects the subjects to be allocated to the control and treatment groups are *nonrandomized concurrent control studies*. The advantages of this simpler trial design are that clinicians do not leave to chance the assignment of treatment in each patient and there is no need for patients to accept the concept of randomization. Implicit in this design type is the assumption that the investigator can appropriately match subjects in the test and control groups for all relevant baseline characteristics. This is a difficult task and can produce a selection bias that may result in conclusions that differ in direction and magnitude from those obtained from RCTs.[36]

Observational analyses contain many of the same structural characteristics as randomized trials except that the treatment is not randomized. These studies should have prospectively collected data with uniform definitions managed by a multidisciplinary group of investigators that include clinicians, biostatisticians, and data analysts. Outcomes must be collected in a rigorous and unbiased fashion, just as in the randomized trial.

Historical Controls

Clinical trials that use historical controls compare a test intervention with data obtained earlier in a *nonconcurrent, nonrandomized control group*. Potential sources for historical controls include previously published medical literature and unpublished data banks of clinic populations. The use of historical controls allows clinicians to offer potentially beneficial therapies to all subjects, thereby reducing the sample size for the study. The major drawbacks are bias in the selection of the control population and failure of the historical controls to reflect contemporary diagnostic criteria and concurrent treatment regimens for the disease under study.

It should be noted, however, that prospectively recorded registry data may be more representative of actual clinical practice than the control groups in RCTs. Notable examples include the National Registry of Myocardial Infarction (NRMI) and CRUSADE registries in the United States and international registries such as GRACE (Global Registry of Acute Coronary Events). Reports from such registries are useful for identifying gaps in translation of therapies proven to be effective in clinical trials into routine practice.[37]

Crossover Design

The crossover design is a special case of the RCT, in that each subject serves as his or her own control. A simple, two-period, crossover design randomly assigns each subject to either the test or control group in the first period and to the alternative in the second period. The appeal of this design is the ability to use the same subject for both test and control treatments, thereby diminishing the influence of inter-individual variability and allowing a smaller sample size. However, important limitations to crossover design are the assumptions that the effects of the treatment assigned during the first period have no residual effect on the treatment assigned during the second period and that the patient's condition remains stable during both periods. The validity of these assumptions is often difficult to verify either clinically or statistically (e.g., testing for an interaction between period and intervention), leading some authorities to discourage the use of crossover designs. One possible use of the crossover trial design is the preliminary evaluation of new antianginal agents for patients with chronic, stable exertional angina.[38]

Withdrawal Studies

In withdrawal studies, patients with a chronic cardiovascular condition are taken off therapy or undergo a reduction in dosage. The goal is to evaluate the response to discontinuation

of treatment or reduction in its intensity. An important limitation is that only patients who have tolerated the test intervention for a period of time are eligible for enrollment, because those with incapacitating side effects would have been taken off the test intervention and are, therefore, not available for withdrawal. This selection bias can overestimate benefit and underestimate toxicity associated with the test intervention. In addition, changes in the natural history of the disease may influence the response to withdrawal of therapy. For example, if a therapeutic intervention is beneficial early after the onset of the disease but loses its benefit over time, the withdrawal of therapy late in the course of treatment might not result in deterioration of the patient's condition. A conclusion that the intervention was not helpful because its withdrawal during the chronic phase of treatment did not result in a worsening of the patient's condition provides no information about the potential benefit of treatment in the acute phase or subacute phase of the illness. Withdrawal trials can provide clinically useful information but they should be conducted with the same standards that are applied to controlled trials of prospective treatment, including randomization and blinding, if possible.

The following withdrawal trial in cardiology illustrates many of the features discussed previously. Although digitalis has been used by physicians for more than 200 years, its benefits for the treatment of chronic congestive heart failure, particularly in the patient with normal sinus rhythm, remain controversial. To assess the consequences of withdrawing digoxin from clinically stable patients with New York Heart Association functional class II to III congestive heart failure who are receiving angiotensin converting enzyme inhibitors, the *R*andomized *A*ssessment of [the effect] *D*igoxin [in patients] on *I*nhibitors of the *AN*giotensin-*C*onverting *E*nzyme (RADIANCE) investigators randomly allocated 178 patients in a double-blind manner to continue to receive digoxin or to switch to a matched placebo.[39] Worsening heart failure necessitating discontinuation from the study occurred in 23 patients who were switched to placebo but in only 4 patients who continued to receive digoxin ($P < 0.001$). The results of the RADIANCE trial seem to indicate that withdrawal of digoxin in patients with mild-to-moderate congestive heart failure as a result of systolic dysfunction is associated with adverse consequences, but it does not provide information on the potential mortality benefit of digoxin when *added* to a regimen of diuretics and angiotensin-converting enzyme inhibitors.[40] The Digitalis Investigation Group (DIG) Trial, a classic RCT, showed that digoxin therapy was not associated with a mortality benefit but did provide symptomatic improvement in that it reduced the need for hospitalization for decompensated congestive heart failure.[41]

Factorial Design

When two or more therapies are tested in a clinical trial, investigators typically consider a *factorial design*, in which multiple treatments can be compared with control through independent randomization within a single trial. A schematic example of a 2 × 2 factorial design trial is shown in Figure 1–3. In this example, 10,000 patients are randomized to receive two interventions (drug A and drug B). There are four categories of patients: active A/active B, placebo A/active B, active A/placebo B, placebo A/placebo B. These groups of patients allow assessment of the treatment effect of drug A in the absence of drug B (difference 1) and in the presence of drug B (difference 2). A grand summary (pooled) statement of the treatment effect of drug A can be made, along with a measure of the interaction of coadministration of drug B and drug A. A similar and symmetrical analysis can be performed for drug B. This line of reasoning may be extended to more than two test treatments—as was the case in the fourth International Study of Infarct Survival (ISIS-4), in which three interventions (i.e., captopril, nitrates, and magnesium) were evaluated in a 2 × 2 × 2 factorial design, and patients fell into one of eight separate categories.[42]

Factorial design trials are more easily interpreted when there is believed to be no interaction between the various test treatments—as is often the case when drugs have unrelated mechanisms of action. If no interactions exist, multiple drug comparisons can be efficiently performed in a single large trial that is smaller than the sum of two independent clinical trials. When interactions are detected, each intervention must be evaluated individually against a control and each of the other interventions in which an interaction exists.

Biostatistical Tools for Comparing Therapies for Acute Coronary Syndromes

Use of Factorial Design to Evaluate Drug Interactions

Total Enrollment = 10,000 patients

	Active A 5000	*Placebo A* 5000
Active B 5000	Active A Active B 2500	Placebo A Active B 2500
Placebo B 5000	Active A Placebo B 2500	Placebo A Placebo B 2500

Evaluation of drug A alone and in combination with drug B:

Active A / Placebo B vs Placebo A / Placebo B = $\text{Difference}_1 = D_1$

Active A / Active B vs Placebo A / Active B = $\text{Difference}_2 = D_2$

Treatment effect of drug A in the absence of drug B = D_1

Treatment effect of drug A in the presence of drug B = D_2

Grand summary of treatment effect of drug A = $D_1 + D_2$

Interaction of drug B on treatment effect of drug A = $D_2 - D_1$

Figure 1–3 Factorial design of clinical trial. *Top*, In this example, 10,000 patients are randomized to receive or not receive two interventions (drug A and drug B). Each patient will fall into one of the following four categories: Active A/Active B, Placebo A/Active B, Active A/Placebo B, Placebo A/Placebo B. *Bottom*, Differences in event rates for the comparisons permit an assessment of the treatment effect of drug A in the presence and absence of drug B. See text for further discussion. (Reproduced with permission from Antman EM: Medical therapy for acute coronary syndromes: An overview. In Califf R, Braunwald E [eds]: Acute Myocardial Infarction and Other Acute Ischemic Syndromes. Philadelphia, Current Medicine, 1996.)

The factorial design trial has an important place in cardiology, in which multiple therapies are typically given to the same patient for important conditions such as MI, heart failure, and secondary prevention of atherosclerosis, and so in practical terms, the factorial design is more reflective of actual clinical practice than trials in which only a single intervention is randomized. Clinicians need to know how much incremental value comes from the administration of one more drug to the patient and whether any drug interactions exist. It is worth noting, however, that it is probably an insurmountable task to rule out the possibility of a drug interaction because of the imprecision with which interaction effects are estimated (i.e., wide confidence intervals), the poor power of tests for statistical significance of interactions between the test interventions, and the vast number of non–protocol-related drugs a patient may receive. For example, in addition to the eight patient groups in the main design of ISIS-4, the type of fibrinolytic prescribed, the presence or absence of intravenous β-blockers, and the use of nontrial nitrates such as intravenous nitroglycerin, among other factors, rapidly escalate the number of patient cells to nearly 100.[42]

Trials That Test Equivalence of Therapies

Advances in cardiovascular therapeutics have dramatically improved the treatment of various diseases, such that several therapies of proven efficacy may coexist for the same treatment. However, it may still be desirable to develop new therapies that are equally efficacious but have an important advantage—such as reduced toxicity, improved patient tolerability, more favorable pharmacokinetic profile, fewer drug interactions, or lower cost.[43,44] Testing such new therapies using placebo-controlled trials poses problems on ethical grounds because one half of the patients would be denied treatment when an accepted therapy of proven efficacy exists.[28,45,46] This has led to a shift in clinical trial design to demonstrate therapeutic equivalence of two treatments rather than superiority of one of the treatments.[27,43,47,48] The concept of equivalence trials has a precedent in the study of bioequivalence, where, for example, two drug preparations are considered equivalent if they produce similar areas under the curve (AUCs) in plots of blood levels versus time.

It is not possible to show two active therapies to be completely equivalent without a trial of infinite sample size. Instead, investigators resort to specifying a value (δ) and consider the test therapy to be equivalent to the standard therapy if, with a high degree of confidence, the true difference in treatment effects is less than δ (Fig. 1–4A).[47,49]

The nomenclature related to trials of tests of equivalence between two therapies can be confusing. In a classic equivalence trial, if the confidence intervals for the estimate of the effects of the two treatments differ by more than the equivalence margin (i.e., δ) in either direction, then equivalence is said not to be present. For most clinical trials of new therapies, the objective is to establish that the new therapy is not worse than the standard therapy (i.e., active control) by more than δ.[45] Such one-sided comparisons are referred to as *noninferiority trials*.[43] The new therapy may satisfy the definition of *noninferiority* but, depending on the results, may or may not actually show superiority compared with the standard therapy.

Specification of the appropriate margin, or δ, is often problematic. Clinicians prefer to set δ based on a clinical perception of a minimally important difference they believe would affect their practice. Regulatory authorities, who are bound by a legal mandate "to show that drugs work," assess the effect of the standard therapy based on prior trials where it was compared with placebo. Rather than specifying the point estimate for the full effect of the standard therapy over placebo, a more conservative approach is taken by selecting the lower bound of a confidence interval for superiority of the standard therapy over placebo for setting the noninferiority margin.[45,50] Because the noninferiority margin is usually smaller than the treatment difference between an active control and placebo, the sample size of noninferiority trials is typically larger than for a superiority trial against placebo.

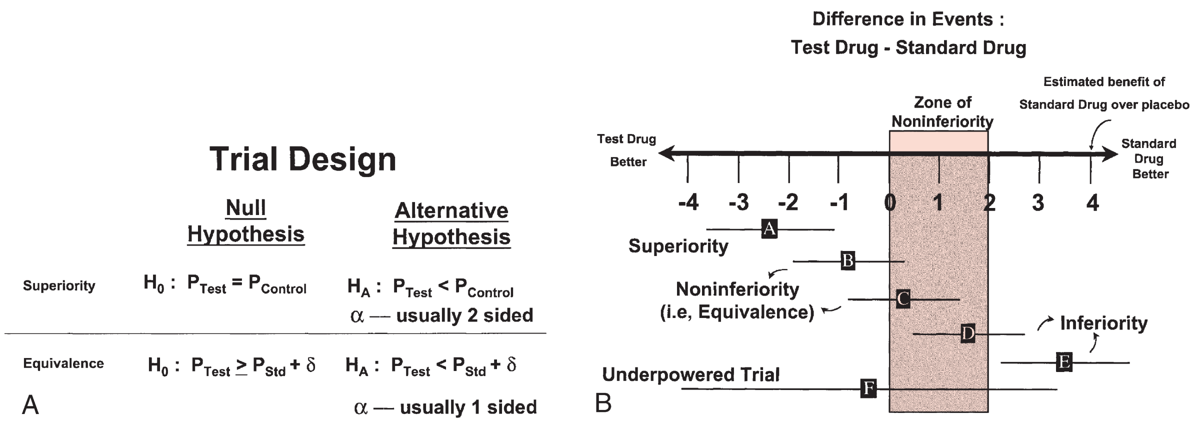


Figure 1–4 **A,** Statistical design of superiority and equivalence trials. In both superiority and equivalence trials, the investigators propose a null hypothesis (H_0) with the goal of the trial being to reject H_0 in favor of the alternative hypothesis (H_A). To determine whether the null hypothesis may be rejected, before initiation of the trial, the type I (α) and type II (β) errors are specified. In superiority trials, α is usually two sided, whereas it is usually one sided in equivalence trials. The quantity (1–β) is referred to as the power of the trial (*not shown*). Std = standard therapy. **B,** Example of design and interpretation of noninferiority trials. The zone of inferiority is prespecified based on prior trials comparing the standard drug with placebo. Examples of hypothetical trials A to F are shown, of which some satisfy the definition of noninferiority. See text for further discussion. (**B,** Redrawn from Antman EM: Clinical trials in cardiovascular medicine. Circulation 2001;103:E101-4.)

Figure 1–4B provides an example of the design of noninferiority trials and interpretation of six hypothetical trial results. In Figure 1–4B, the difference in events between the test drug and the standard drug is plotted along the horizontal axis. Based on trials against placebo, the standard drug provides a benefit over placebo at the +4 position, but the lower bound of its superiority over placebo is at the +2 position. Thus, the noninferiority margin is set at +2. The six hypothetical trials A to F are shown with the point estimate of the difference between the test drug and standard drug as filled squares and the width of the 95% CI for the difference as the thin horizontal lines. Because the results of trial A fall entirely to the left of 0 (i.e., the upper bound does not enter the zone of noninferiority), it is possible to declare the test drug to be superior to the standard drug. In the trials B and C, the upper bound falls within the zone of noninferiority, and in loose parlance, the test drug is declared to be "equivalent" to the standard drug. Note that in the cases of trials D and E, the noninferiority requirement is not satisfied (upper bound exceeds margin in trial D, and the entire confidence interval exceeds the margin in trial E), and the test drug is said to be inferior to the standard drug. It is important to prespecify the noninferiority margin before starting the trial because if it is specified after the results are known, the trial could be criticized owing to potential subjective bias. For example, if the results of trial D were known and the noninferiority margin was set at +3 rather than +2, the test drug would satisfy the definition of noninferiority but such an approach would be highly suspect. It is also important to have a sufficient sample size of the trial to draw meaningful conclusions. For example, although the point estimate for trial F is in favor of the test drug, the wide confidence intervals are due to a small sample size. Trial F does not allow the investigators to claim superiority of the test drug compared with the standard drug, and it would be inappropriate to claim it to be "equivalent" to the standard drug simply because superiority could not be demonstrated (note that the upper bound of trial F clearly exceeds the noninferiority margin).

Investigators can prespecify that a trial is being designed to test superiority and noninferiority simultaneously.[50,54] For a trial that is configured only as a noninferiority trial, it is acceptable to test for superiority at the conclusion of the trial. However, because of the subjective bias as mentioned, the reverse is not true—trials configured for superiority cannot later test for noninferiority unless the margin was prespecified.[50] An important commonality between superiority and noninferiority trials is that the clinical experts involved in trial design should consciously consider the minimally important clinical outcome difference. A common understanding of the difference between outcomes with two therapies forms the basis for providing the appropriate perspective on the interpretation of test statistics—in essence, the difference between "statistically significant" and "clinically important" is determined by the common view of the difference that would lead to a change in practice. Noninferiority trials, a more recent addition to the RCT repertoire, are prone to controversy, especially if there is disagreement over the noninferiority margin (i.e., the percentage of the treatment benefit of the gold standard therapy over placebo that would be retained by the new treatment and still be considered clinically equivalent).[51,51a] The reporting of noninferiority trials in the medical literature is often deficient, with failure to provide an adequate justification for the noninferiority margin or the sample size.[52] In a fashion similar to that for reporting a superiority trial, the CONSORT Group has published recommendations for a checklist and graphic display of the results of noninferiority trials.[53]

Selection of Endpoint

A critical decision when designing a clinical trial is the selection of the outcome measure. In trials comparing two treatments in cardiovascular medicine, the outcome measure (or endpoint of the trial) is characteristically a clinical event. The characteristics of an ideal primary outcome measure are that it is easy to diagnose, is free of measurement error, can be observed independent of treatment assignment, is clinically relevant, and should be selected prior to the start of data collection for the trial.[55] Because of their serious nature, the hard endpoints of mortality (all cause or cardiovascular) and nonfatal events such as myocardial infarction have traditionally been selected by cardiovascular investigators for definitive evaluation of new treatments, especially in registration pathway trials.[34,54]

Improvements in cardiovascular treatments have, gratifyingly, lead to a reduction in mortality rates and, therefore, a lower event rate in the control arm of clinical trials—with an attendant increase in the required sample size (see later). The desire to evaluate new therapeutic approaches in the face of rising costs to conduct large clinical trials has resulted in two major approaches to the selection of endpoints. The first is to use a composite endpoint combining mortality with one or more nonfatal negative outcomes such as myocardial infarction, stroke, recurrent ischemia, or hospitalization for heart failure.[56-59] Trials with a logical grouping of composite endpoints that are likely to each be affected by the treatments being studied are clinically valuable and have been used to advance treatments for heart failure and acute coronary syndromes.[15] However, interpretation of composite endpoints becomes problematic when elements of a composite endpoint go in opposite directions in response to treatment (e.g., reduced mortality but increased nonfatal MI). To date, there is no consensus on an appropriate weighting scheme for composite endpoints.[15]

Another approach is to use a surrogate endpoint as a substitute for clinical outcomes. A valid surrogate endpoint not only must be predictive of a clinical outcome but also evidence that modification of the surrogate endpoint captures the effect of a treatment on clinical outcomes because the surrogate is in the causal pathway of the disease process.[15] Examples of a successful surrogate endpoint and failed surrogate endpoints are schematically illustrated in Figure 1–5. Whether or not a surrogate endpoint is useful for determining if a treatment is efficacious, a single surrogate cannot be used to develop a balanced view of risk and benefit, particularly compared with alternative therapies. This increasingly recognized critical element of therapeutic development and evaluation requires measurement of clinical outcomes in the relevant population over a relevant period of time.

Sample Size Estimations and Sequential Stopping Boundaries

Estimation of the sample size for trials involves a statement of the scientific question in the form of a null hypothesis (H_0) and an alternative hypothesis (H_A). For example, in the case of

dichotomous variables (e.g., presence or absence of a primary outcome variable such as mortality), the null hypothesis states that the proportion of patients dying in the test group (P_{Test}) is equal to that in the control group ($P_{Control}$) (see Fig. 1–4A), such that for

$$H_0: P_{Test} - P_{Control} = 0$$

The alternative hypothesis is that for

$$H_A: P_{Test} - P_{Control} \neq 0$$

False-Positive and False-Negative Error Rates and Power of Clinical Trial

To determine whether the null hypothesis may be rejected, before initiation of the trial, the type I (α) and type II (β) errors, sometimes referred to as the *false-positive* and *false-negative rates*, are specified (see Fig. 1–4A). The conventional α of 5% indicates that the investigator is willing to accept a 5% likelihood that an observed difference as large as projected in the sample size calculation occurred by chance and would lead to rejection of the null hypothesis when, in fact, the null hypothesis was correct.[60] The β value reflects the likelihood that a specified difference might be missed or not found to be statistically significant because of an insufficient number of events in the trial at the time of analysis. The quantity (1–β) is referred to as the *power of the trial* and quantifies the ability of the trial to find true differences of a given magnitude between the groups. The relations among estimated event rates, the prespecified α level, and desired power of the trial determine the number of patients that must be randomized to detect the anticipated difference in outcomes according to standard formulas.[60] Similar concepts are applied to response variables that are not dichotomous but are measured on a continuous scale (e.g., blood pressure) or represent time to failure (e.g., Kaplan-Meier survival curves).[61]

Statistical methods are also available for monitoring a trial during the patient recruitment phase at certain prespecified intervals to determine whether the accumulated evidence strongly suggests an advantage of one treatment in the trial.[26] During such interim checks of the data, the differences between treatment groups expressed as a standardized normal statistic (Z_i) are compared with boundaries such as those shown in Figure 1–6. If the Z_i statistic falls outside the boundaries at an *i*th interim look, the DSMB may give serious consideration to recommending termination of the trial. Typically, the data are arranged as *test:control*, so crossing of the upper boundary denotes statistically significant superiority of the test therapy over control, and crossing of the lower boundary denotes superiority of the control therapy over the test therapy. Because of the considerable expense of large clinical trials, in some cases it may be desirable to discontinue a trial at an interim analysis if the accumulated data suggest the probability of a positive result—should the trial proceed to completion—has become quite low. A *futility index* that describes the likelihood of a positive result based on accumulated data has been developed, allowing investigators to discontinue a nonproductive trial and concentrate limited resources on alternative trial options.[63]

Considerable clinical and statistical wisdom is required of DSMB members because they must consider and integrate the consistency and timeliness of the trial data reviewed at each interim analysis, random variation in event rates during the course of the trial, the type and severity of the disease under study, the magnitude of the benefit versus the risks of the therapy being investigated, and emerging data from other trials and clinical experience.[64] The decision to stop an RCT early because of an apparent strong treatment benefit favoring one of the arms is complex. Although investigators, sponsors funding the trial, and journal editors are likely to become

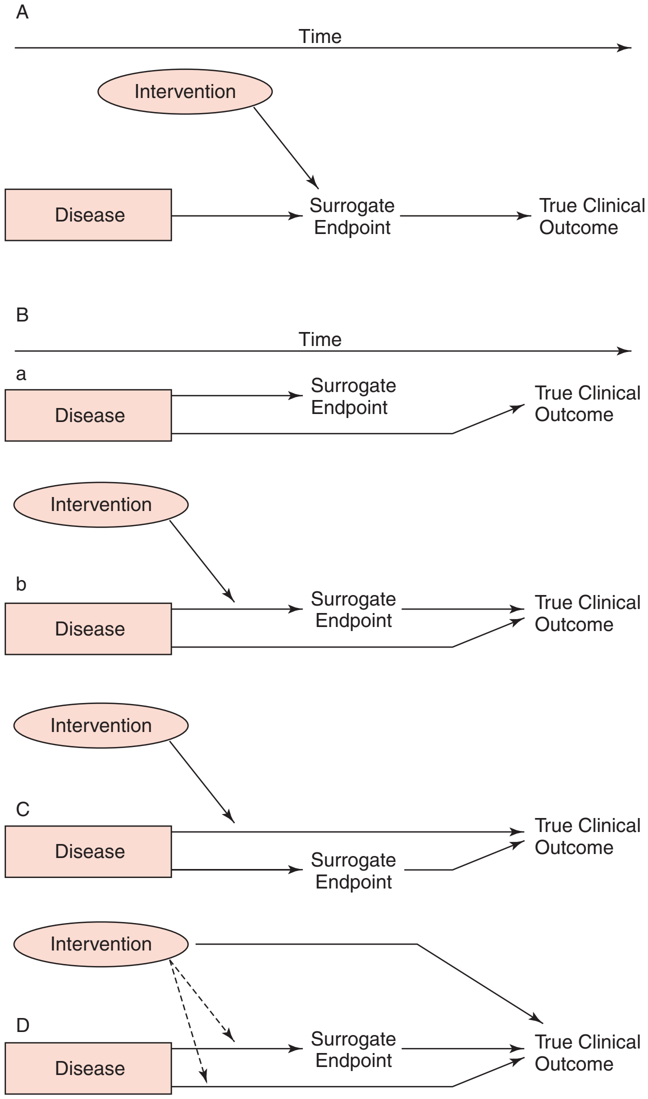


Figure 1–5 The setting that provides the greatest potential for the surrogate endpoint to be valid (a). Reasons for failure of surrogate endpoints (b). The surrogate is not in the causal pathway of the disease process (**A**). Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate (**B**). The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect (**C**). The intervention has mechanisms for action independent of the disease process (**D**). *Dotted lines* indicate mechanisms of action that might exist. (Redrawn with permission from Fleming TR, DeMets DL: Surrogate endpoints in clinical trials: Are we being misled? Ann Intern Med 1996;125:605-13.)

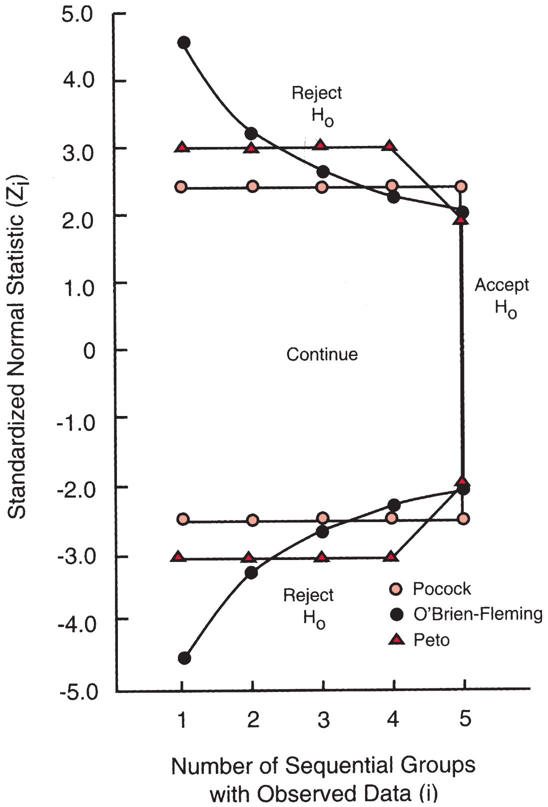


Figure 1–6 Sequential stopping boundaries used in monitoring a clinical trial. Three sequential stopping boundaries for the standardized normal statistic(Z_i) for up to five sequential groups (of patients in enrolled in trial by the *i*th analysis) with final two-sided significance level of 0.05. (Reproduced with permission from Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials,4th ed. New York, Springer Verlag, 1998.)

caught up in the excitement and publicity surrounding an announcement of early stopping of a trial for benefit, it should be noted that there is a precedent for unrealistically large treatment effects to be disproved by subsequent RCTs.[65,66] A systematic review of RCTs stopped early for benefit reported that there is often a failure to report relevant information about the decision-making process and such decisions to stop an RCT early tend to provide unrealistic estimates of the true treatment benefit when the total number of events observed is small.[66] In the case of new, unapproved treatments, early stopping for benefit may place regulatory authorities in the uncomfortable position of not having enough safety data on which to base approval of the new treatment.[65]

Although it may occasionally appear that an extreme treatment effect is present in a particular subgroup, this must be interpreted cautiously to be certain that this effect is consistent with a prior hypothesis and remains significant after adjusting for multiple comparisons, interactions, and the interim nature of the analysis.[67] DSMB members must balance formal statistical stopping guidelines, ethical obligations to patients, common sense, and the obligation to the clinical community to ensure that the willingness of patients to consent to participation in the trial leads to an advance in the state of knowledge about the optimal therapeutic strategy.[31] For example, in 1989, the Beta-Blocker Heart Attack Trial was stopped early because of strong evidence of benefit from propranolol, especially in view of the previously published Norwegian Timolol Study.[31] In contrast, CAST was terminated early after the DSMB believed compelling evidence had accumulated indicating that, contrary to the prevailing clinical impression at the time, the suppression of ventricular premature beats with encainide or flecainide after MI was associated with increased mortality rates.[26]

A fascinating and controversial approach to the design, monitoring, and interpretation of clinical trials is the use of a Bayesian approach. Compared with the *classic* or *frequentist* approach described earlier, Bayesian methods formally use prior information specifying it as a prior probability distribution.[68] Instead of presenting the results of the trial in the form of *P* values and confidence intervals, Bayesian analysts present plots of the posterior distribution of the treatment effect. Interim monitoring procedures such as those shown in Figure 1–6 for the frequentist approach are replaced with posterior distribution plots. By employing a "skeptical" prior probability, a conservative approach to stopping rules can be developed according to Bayesian analysis. At present, the frequentist approach is the standard approach accepted by regulatory authorities for the approval of new therapies because of concerns about the sources and uncertainties regarding the prior probability distribution, but particularly with devices, flexibility on this matter is increasing. In the future, a Bayesian approach may be used more frequently in RCT design and analysis.

HOW TO READ AND INTERPRET A CLINICAL TRIAL

To properly interpret a clinical trial report and to apply it in their practice, clinicians must have a working knowledge of the statistical and epidemiologic terms used to describe the results. By asking three main sets of questions, such as those in Table 1–4 adapted from the McMaster Group, and by summarizing the trial findings as per the example in Figure 1–7, physicians will be equipped to integrate the information in manuscripts that describe clinical trials into their own practices.

One first determines that the study was of sufficient caliber to provide valid results, extracts the essential trial data, and enters it into a 2 × 2 table. In the example shown in Figure 1–7, 10,000 patients who met the enrollment criteria for a clinical trial were randomized with an allocation ratio of 1:1, so 5000 patients received treatment A and 5000 received treatment B. Because only 600 primary outcome events occurred in group A (12% event rate) and 750 occurred in group B (15% event rate), it appears that treatment A is more effective than treatment B.[6] Is this difference statistically significant, and is it clinically meaningful? When the data are arranged in a 2 × 2 table (see Fig. 1–7), a χ^2 test or Fisher exact test can be readily performed according to standard formulas.[9]

Although the investigators of the trial will likely have analyzed the results using one of the methods illustrated in Figure 1–7, it is useful to have a measure of the precision of the findings and an impression of the potential impact of the results on clinical practice. Even a well-designed clinical trial can provide only an estimate of the treatment effect of the test

Table 1–4 Questions to Ask When Reading and Interpreting the Results of a Clinical Trial

Are the Results of the Study Valid?

Primary Guides

1. Was the assignment of patients to treatment randomized?
2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?
    - Was follow-up complete?
    - Were patients analyzed in the groups to which they were randomized?

Secondary Guides

1. Were patients, their clinicians, and study personnel "blind" to treatment?
2. Were the groups similar at the start of the trial?
3. Aside from the experimental intervention, were the groups treated equally?

What Were the Results?

1. How large was the treatment effect?
2. How precise was the treatment effect?

Will the Results Help Me in Caring for My Patients?

1. Does my patient fulfill the enrollment criteria for the trial? If not, how close is my patient to the enrollment criteria?
2. Does my patient fit the features of a subgroup in the trial report? If so, are the results of the subgroup analysis in the trial valid?
3. Were all the clinically important outcomes considered?
4. Are the likely treatment benefits worth the potential harm and costs?

Adapted from material in Guyatt GH, Sackett DL, Cook DJ: The Medical Literature: Users' Guides to the Medical Literature: II. How to Use an Article About Therapy or Prevention: A. Are the Results of the Study Valid? JAMA 1993;270:2598-2601 and Guyatt GH, Sackett DL, Cook DJ: The Medical Literature: Users' Guides to the Medical Literature: II. How to Use an Article About Therapy or Prevention: B. What Were the Results and Will They Help Me in Caring for My Patients? JAMA 1994;271:59-63.

intervention owing to random variation in the sample of subjects studied, who are selected from the entire population of patients with the same disease. The imprecision of the statement regarding treatment effect can be estimated and incorporated into the presentation of the trial results by calculating the 95% CIs around the observed treatment effect.[69] If the 95% CIs are not reported in the trial, inspection of the *P* value may be useful to indicate whether the confidence interval spans a null effect. Alternatively, the 95% CIs may be estimated as the treatment effect plus or minus twice the standard error of the treatment effect (if reported) or calculated directly.[69]

Measures of Treatment Effect

When the outcome is undesirable and the data are arranged as test group:control group, a relative risk (RR) or odds ratio (OR) of less than 1 indicates benefit of the test treatment. The relative risk of 0.80 (95% CI, 0.72 to 0.88) and odds ratio of 0.77 (95% CI, 0.69 to 0.87) in Figure 1–7 are indicative of benefit associated with treatment A.[6] When the control rate is low, the OR will approximate the RR, and the OR may be thought of as an estimator of the RR. As the control rate increases, the OR deviates further from the RR, and clinicians should rely more on the latter. The *treatment effect*, expressed as an RR reduction in this example, is 20%, but its 95% CI ranges from 12% to 28%. Such statements should be interpreted in the context of the absolute risk of the adverse outcome it is designed to prevent. The *absolute risk difference* (ARD) is even more meaningful if expressed as the number of patients that must be treated (=1/ARD) to observe the beneficial effect if it is as large as reported in the trial.[70]

If practitioners are given clinical trial results only in the form of RR reduction, they tend to perceive a greater effectiveness of the test intervention than if a more comprehensive statement is provided, including ARD and the number needed to treat.[71] Thus, in light of the baseline risk of 15% in the control group (a value that might represent the 1-month mortality of contemporary patients with MI not treated with fibrinolytic agents), the 12% event rate in the test group represents an ARD of 3%, which corresponds to 1/0.03 or approximately 33 patients who require treatment to prevent the occurrence of one adverse event. This statement is sometimes given as the number of lives saved per 1000 patients treated, corresponding to 30 lives in this example. Against this benefit must be weighed the risks associated with treatment (e.g., hemorrhagic stroke with fibrinolytic therapy for MI), which can be expressed as the *number needed to harm* (NNH = 1/ARI, where ARI is the absolute increase in events in the treatment group).[72] A composite term referred to as *net clinical benefit* has been introduced to incorporate both benefit and harm. In this example, if treatment A is associated with a 0.5% excess risk of an adverse outcome, such as stroke, compared with treatment B, then for every 1000 patients who receive treatment A, 30 lives would be saved at the expense of five strokes, for a net clinical benefit of 25 stroke-free lives saved.

These types of comparisons require the clinical community to make a judgment regarding the relative importance of various outcomes. How many deaths have to be prevented to offset one stroke? Another example is the possibility that some therapies (inotropic agents) may improve symptoms but at the same time may increase mortality rates, a scenario that may be acceptable to patients incapacitated by severe symptoms but not to patients with mild symptoms.[15] This issue can be explicitly addressed with the use of decision analysis (see Decision Analysis section).

The *number needed to treat* is a complex concept that becomes even more difficult when the impact of therapies for chronic disease are considered. For acute therapies with only a short-term effect, such as thrombolytic therapy, the simple version of number needed to treat is adequate. However, saving 10 lives per 100 patients treated in the first 30 days is quite different from the same effect over 5 years. In some therapies, the concept is even more complex, because the more effective treatment may have an early hazard—leading to a reversal of the treatment effect over time.

When weighing the evidence from clinical trials for a treatment decision in an individual patient, physicians must

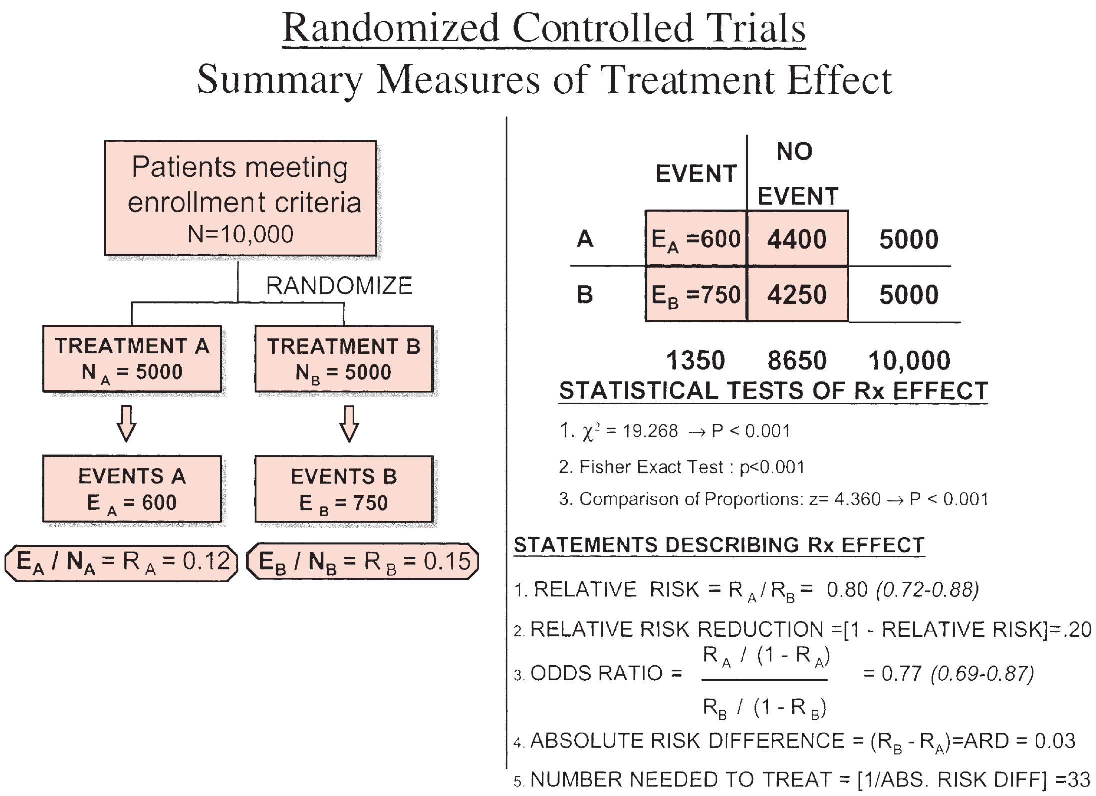


Figure 1–7 Evaluation of a clinical trial. In this example, 10,000 patients meeting enrollment criteria for the randomized controlled trial (RCT) are randomized such that 5000 patients receive treatment A and 5000 patients receive treatment B. Six hundred patients assigned to treatment A experience an event (e.g., death) yielding an event rate of 12%, compared with 750 patients assigned to treatment B, yielding an event rate of 15%. The 2 × 2 table (*right*) is then constructed, and various statistical tests are performed to evaluate the significance of the difference in event rates between group A and group B. Common statements describing the treatment effect are the relative risk (of events in treatment A versus treatment B); the odds ratio (for development of events in treatment A versus treatment B), or the absolute risk difference (of events in treatment A versus treatment B) using the formulas shown. A clinically useful method of expressing the results is to calculate the number of patients that need to be treated to prevent one event. (Adapted from Antman EM: Clinical trials in cardiovascular medicine. Circulation 2001;103:E101-4.

consider more than the level of significance of the findings.[73] In addition to the rationale for a given treatment, practitioners need to know which patients to treat, what drug and dose to use, and when and where therapy should be initiated. Not all clinical trial reports provide all information required to form a complete assessment of the validity, precision, and implications of the results and answers the questions noted previously.[74] In addition, clinicians are cautioned against overinterpreting subgroup analyses from RCTs. Most RCTs lack sufficient power to adequately assess treatment effects in multiple subgroups; repeated statistical testing across several subgroups can lead to false-positive findings by chance, and it is, therefore, preferable to present subgroup results in a graphic format depicting the point estimate and confidence intervals to illustrate the range of possible treatment effects.[75] In an attempt to introduce consistency in the reporting of clinical trials in the biomedical literature, a checklist of information for trialists, journal editors, peer-review panels, and the general medical audience was proposed (Table 1–5).[76] The presentation of a minimal set of uniform information in clinical trial reports should assist clinicians in making treatment decisions.[77]

Detection of Treatment Effects in Clinical Trials

The interplay of a variety of factors influences the ability of investigators to detect a treatment effect (benefit or harm) in a clinical trial (Fig. 1–8). Variables set by investigators during the design of a clinical trial include (1) the definition of events that constitute the trial endpoints (e.g., a hard endpoint such as death is infrequent, resulting in fewer events observed compared with a composite endpoint); (2) the duration of follow-up—short-term follow-up limits the time during which events may occur and reduces the likelihood of detecting harm; and (3) sample size—an inadequate sample size places investigators at the risk of a large type II error and failure to detect a treatment effect when one exists.[72]

Variables related to both the patient and the treatment being investigated influence the relative difference in events in the treatment groups and may minimize or magnify the signal of increased risk of events. These include: (1) the risk of events in the control group—the impact of the test treatment may be less evident in healthier subjects where relatively few events occur in the control group; (2) the relative risk of events in

Table 1–5 Checklist of Information for Inclusion in Reports of Clinical Trials

Introduction

A priori hypothesis, specific protocol objectives

Methods

Study As Designed Includes

- Planned study population, including controls
- Inclusion and exclusion criteria
- Planned subgroup analyses
- Prognostic factors that may affect study results
- Outcome measures and minimum difference(s) to be considered clinically important
- Planned treatment interventions
- Method of assignment of subjects to treatments (for example, randomization method, blinding or masking procedure, matching criteria)
- Planned sample size, power calculations
- Rules for stopping the study
- Methods of statistical analysis in sufficient detail to permit replication

Results

Study As Conducted Includes

- Inclusive dates of accrual of study population
- Sample size achieved
- How many subjects were excluded or withdrew and the reasons
- Demographics and clinical characteristics of the study population, including controls
- How the study as conducted deviated from the study as planned and the reasons (for example, compliance)

Study Findings Include

- Estimates of treatment effects, stated as comparisons among treatment groups (for example, differences in risks, rates, or means of outcome measures, as well as exact P values, not just $P < .05$)
- Measures of precision for outcome measures and for estimates of treatment effects (confidence intervals, standard errors)
- Summary data and appropriate descriptive statistics
- Complications of treatment
- Repository where original data can be obtained

Discussion

- Interpretation of study findings
- Results considered in the context of results in other trials reported in the literature

Modified from Working Group on Recommendations for Reporting of Clinical Trials in Biomedical Literature. Call for Comments on a Proposal to Improve Reporting of Clinical Trials in the Biomedical Literature. Ann Int Med 1994;121:894-95.

the treatment group—this is related both to the intrinsic properties of the treatment being investigated and the choice of the comparator arm (e.g., a treatment effect is more easily detected if the comparator arm is placebo and less readily detected in trials with an active comparator); (3) and interactions with other treatments. If the test treatment improves symptoms or biomarker measurements relative to control, the control group may be exposed to more counterbalancing beneficial therapies, a phenomenon described as intensification. Although this cannot be prevented ethically, consideration of this issue in trial design and monitoring during the study can minimize the impact of intensification.

To complicate the situation further, the interface of the patient and the treatment may change over the course of exposure to the treatment. For example, development of diabetes or worsening hypertension may culminate in disruption of a high risk or vulnerable plaque with the development of a superimposed thrombus. As the acute situation evolves, the risk in the control arm may change and the relative risk associated with a drug may also change—both in an adverse direction.

These considerations assume particular importance when assessing whether a signal of harm is present with a given treatment (e.g., the cardiovascular risks associated with coxib use).[72] One may depict the relation among the risk of events in the control group (control event rate, CER), the relative risk of events with a particular drug (RR), and the NNH (critically related to the ability to detect a signal of harm), related to each other by the formula: $NNH = 1/ [(RR - 1) \cdot CER]$. The surface shown in Figure 1–9 rises steeply to a high NNH (difficulty in detecting harm) with a low rate of events in the control group and/or low relative risk in the treatment group. The ability to detect harm improves as NNH drops with increasing rates in the control arm and/or increasing relative risk in the treatment arm (see Figs. 1–8 and 1–9).

When administering therapies that have a beneficial effect but are associated with serious potential for harm, the general goal is to operate on the steep portion of the surface in Figure 1–9, thereby minimizing patient risk. This can be accomplished by preferentially prescribing treatments (e.g., coxibs) only to patients at low risk of events (i.e., moving to lower rates of events in the control group in Fig. 1–9). Selecting drugs with a lower risk of harmful events and minimizing the dose and duration of treatment are also advisable (i.e., moving to a lower relative risk in Fig. 1–9).

META-ANALYSIS

Frequently, clinicians are faced with many trials of a given treatment, some of which provide seemingly conflicting results. A method of summarizing the data is needed. *Meta-analysis* is a systematic, quantitative synthesis of data from multiple clinical sources that address a related question. Meta-analysis is a well-defined, scientific statistical discipline with established methods and standards. Synonymous terms encountered in the literature include *overview*, *pooling*, *data pooling*, *literature synthesis*, *research synthesis*, and *quantitative review*. Although the concept of data pooling has existed since the early 1900s, its introduction into clinical literature has met with mixed reactions, ranging from exuberant support and in-depth analysis to overt skepticism. The large number of meta-analyses published in the field of cardiovascular medicine suggests that the technique is gaining in popularity and is likely to play an important role in the complex process of therapeutic decision-making in the future, as well as in regulatory approval of new drugs and devices used in cardiology.[78-82] Authoritative bodies have begun to establish

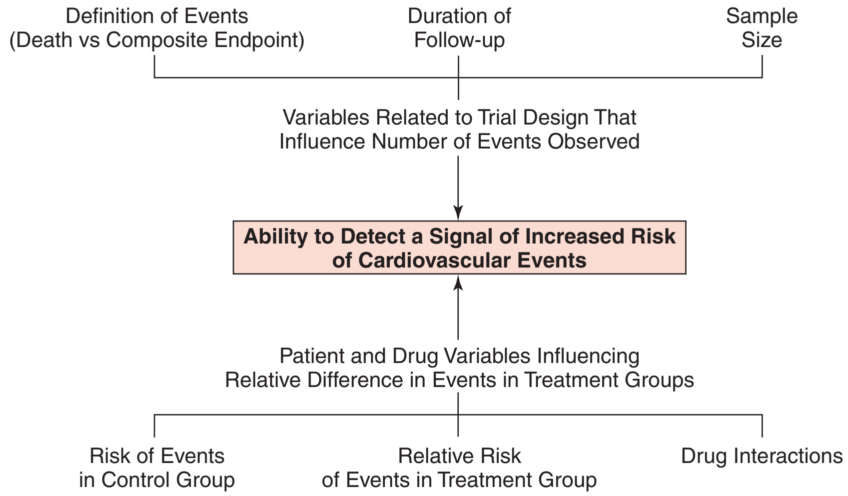


Figure 1–8 Detection of treatment effects in clinical trials. Factors related to trial design (*top*) and to the patient and drug being investigated (*bottom*) are shown. The interplay of these factors influences the ability to detect a treatment effect in a clinical trial. (Redrawn from Antman EM, DeMets D, Loscalzo J: Cyclooxygenase inhibition and cardiovascular risk. Circulation 2005;112:759-70.)

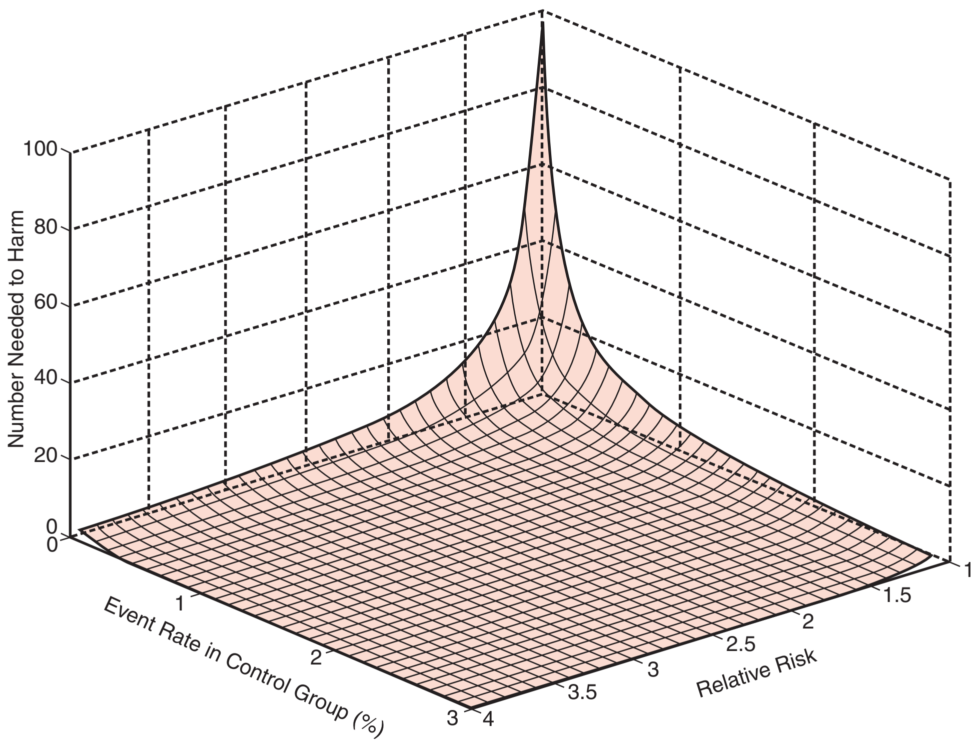


Figure 1–9 The relation of the event rate in the control group and relative risk of cardiovascular events with the treatment being investigated determines the number of patients who need to be treated with the drug to observe one cardiovascular event (Number Needed to Harm). The surface generated can be used to understand the relative ease or difficulty of detecting a signal of harm with a particular treatment (e.g., coxibs). (Redrawn with permission from Antman EM, DeMets D, Loscalzo J: Cyclooxygenase inhibition and cardiovascular risk. Circulation 2005;112:759-70.)

standards for improving the quality of reports of meta-analyses of clinical trials (QUOROM = *QU*ality *O*f Reporting *O*f *M*eta-analyses),[83] and observational studies (MOOSE = *M*eta-analysis *O*f *O*bservational Studies in Epidemiology).[82] Meta-analysis software is available both commercially and on several public domain Web sites.[84]

When pooling studies, it is important that all available trials are located and considered for inclusion. Because investigators are more likely to report only positive findings, the issue of publication bias must be considered when searching for trials to include in a meta-analysis.[85] Statistical techniques have been proposed to screen for publication bias, although this appears to be more of a concern for observational and laboratory-based experimental studies than for RCTs.[86]

The fundamental principle of a meta-analysis is that the statistical power to estimate a treatment effect is enhanced because of an increase in sample size. An inherent assumption is that the available studies are sufficiently similar that pooling is appropriate. The various techniques of pooling construct a weighted average of the study outcomes; the selection of weighting techniques and the approach to handling between-study variability distinguish the different analytic methodologies.[87] Some authorities have proposed incorporating an adjustment for variations in the quality of individual trials when performing a meta-analysis, but this requires further research before formal recommendations can be made.[88]

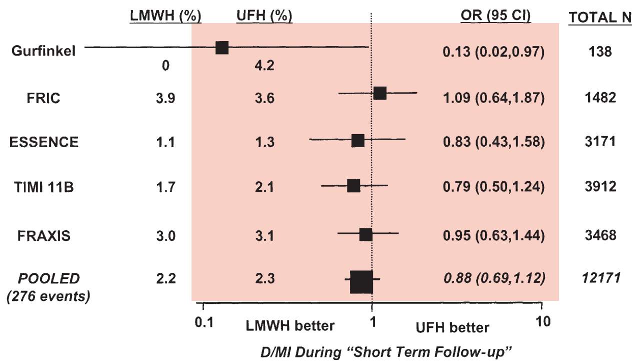
Another important dimension of meta-analysis is the composite overview of therapies considered to be in the same "class." Particularly in the formulation of clinical practice guidelines, the general policy has been to review data for all members of the same class, and then to make a

recommendation about the class rather than individual compounds or devices. In cardiovascular therapeutics, controversy has arisen concerning the antiplatelet agent, statin, low molecular weight heparin, and β-blocker classes and whether the risks and benefits of the many available agents are similar for them to be "lumped together."[89]

The low-molecular-weight heparins provide an excellent example of the difficulty involved in this issue. By lumping together all members of the class, the American College of Cardiology/American Heart Association Guidelines Committee on the Management of Patients with Unstable Angina was able to make a statement that low-molecular-weight heparins are superior to no antithrombin therapy.[89] However, when low-molecular-weight heparins are compared with unfractionated heparin, if all trials are pooled, there is no clear advantage for low-molecular-weight heparins compared with unfractionated heparin (Fig. 1–10A).[90] However, when data for the low-molecular-weight heparin enoxaparin are separated from the remaining data, enoxaparin is seen to be significantly superior to unfractionated heparin (see Fig. 1–10B).[89,90] Although testing for heterogeneity is a quantitative tool to guide investigators as to the advisability of "lumping" versus "splitting," the test is not powerful, and additional tools are needed to sort out the development of quantitative estimates about class effect versus the attributes of individual therapies.

Principles of Pooling Studies

The *fixed-effects model* (Fig. 1–11) assumes that the trials are sampled from a homogeneous group. Under the homogeneity assumption, each trial provides an estimate of the single true treatment effect, and differences between the estimates from the various trials are the result only of experimental error (*within-trial variability*). The *random-effects model* assumes that the trials are heterogeneous and that differences among the various estimates of the treatment effect are due to both experimental error (*within-trial variability*) and differences among the trials, such as trial design and characteristics of the patients enrolled (*between-trial variability*). The random-effects model is generally favored because heterogeneity that cannot be explained by experimental error often exists among trials, and this model takes such heterogeneity into account in estimation and hypothesis testing.[91] Unless extreme heterogeneity is present among the trials, the point estimate of the treatment effect is similar using fixed- and random-effects



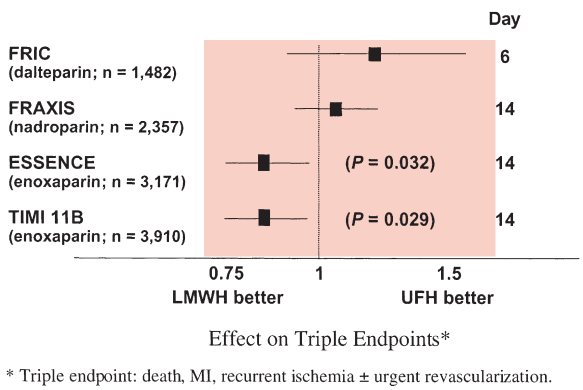


Figure 1–10 Examples of the complexity of pooling studies of multiple drugs within a class. Several different low-molecular-weight heparin (LMWH) preparations have been studied in patients with unstable angina/non ST-segment elevation myocardial infarction (MI). Although there is general agreement that LMWHs are superior to placebo for reducing death and cardiac ischemia events, controversy exists when LMWHs are compared with unfractionated heparin (UFH). **A,** Results of five trials of three different LMWHs versus UFH are plotted individually and then pooled under the assumption that they exhibit a class effect with little heterogeneity among the findings of the various trials. The pooled analysis shows a point estimate favoring LMWH for reducing death/MI during short-term follow-up, although the confidence intervals are wide (owing to the low rate of events that occurred among the 12,171 patients at the time of ascertainment of the endpoint) and overlap unity, and the authors concluded there was no evidence of the superiority of LMWHs over UFH. **B,** The four large phase III trials of three different LMWHs are plotted individually. Note that the endpoint analyzed is a composite of death/MI/recurrent ischemia ± urgent revascularization and is ascertained at a later time point (6 to 14 days) than in **A**—two modifications that increase the power of the meta-analysis to discern differences among the LMWHs. Given the biochemical differences among the LMWHs and subtle but potentially important differences in trial design, the results were not pooled into a composite statement of LMWHs versus UFH. Two trials with enoxaparin show it to be significantly superior to UFH, whereas such a finding is not seen in the trials of dalteparin or nadroparin. ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI; FRAXIS, Fraxiparine in Ischemic Syndrome; FRIC, FRagmin In unstable Coronary artery disease; OR, odds ratio; TIMI, Thrombolysis In Myocardial Infarction. (Adapted from Eikelboom JW, Anand SS, Malmberg K, et al: Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: A meta-analysis. Lancet 2000;355:1936-42 and Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on the Management of Patients with Unstable Angina]. J Am Coll Cardiol 2000;36:970-1062.)

models, but the 95% CIs are generally wider with the random-effects method because they incorporate the uncertainty present in the among-trial variation (see Fig. 1–11).[21]

Cumulative Meta-analysis

Some analysts have incorporated a Bayesian approach to synthesis of the results of RCTs.[92] In an effort to shorten the time delay between the identification of an effective or ineffective therapy in clinical trials and translation of the findings into clinical practice, a related technique of continuously updating meta-analyses has been developed. This methodology, referred to as *cumulative meta-analysis*, updates the pooled estimate of the treatment effect each time the results of a new trial are published (Figs. 1–12 and 1–13).

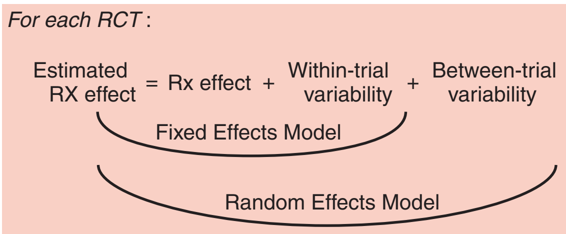


Figure 1–11 Fixed-effects and random-effects models for pooling results of randomized clinical trials (RCTs) in a meta-analysis. The fixed-effects model assumes that the trials are homogeneous and differences between their estimates of the true treatment (Rx) effect are due only to experimental error (within-trial variability). The random-effects model assumes that the trials are heterogeneous and that differences between estimates of the treatment effect are due to experimental error (within-trial variability) and differences among the trials (between-trial variability).

Cumulative meta-analysis is rooted in a Bayesian framework, because it provides the history of the evolution of the posterior probability distribution of clinical trial results and allows one to quantify changes in beliefs about treatment effects as the data accumulate.[141] When cumulative meta-analyses on RCTs of therapies for acute and secondary MI were compared with the textbook chapters and review articles, discrepancies were detected between the meta-analytic patterns of effectiveness and the recommendations of clinical experts.[93] The reasons for these discrepancies may be complex and include a limited ability of authors of review articles to keep abreast of all the RCTs in a particular area; failure to recognize the limited power of small "negative" trials; unfamiliarity or uncertainty about meta-analyses; and a natural conservatism about recommending new therapies until extensive, large-scale clinical trials are completed. The use of cumulative meta-analysis in formulating therapeutic guidelines in the future requires additional methodological study before its role can be properly defined. *Simulation studies* suggest that there may be considerable sampling variation in the time when a cumulative meta-analysis is first significant.[94] Simulation methods can also estimate the type I error and power of a meta-analysis.[94] Because of the possibility in

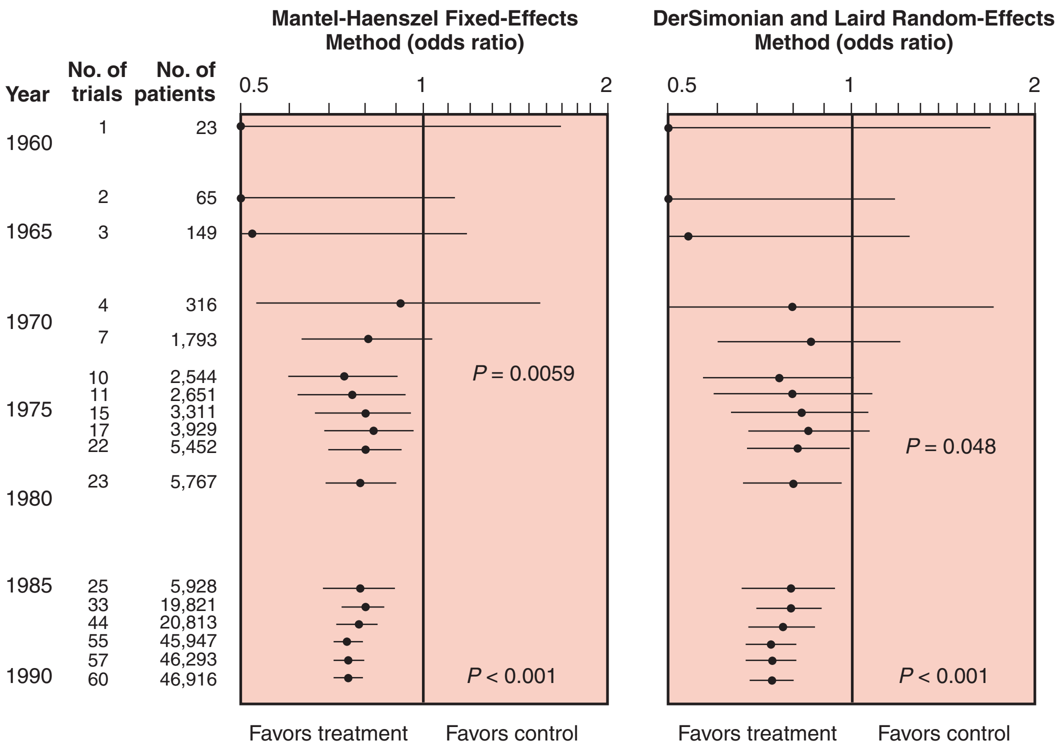


Figure 1–12 Cumulative meta-analyses of 60 trials of intravenous thrombolytic agents for myocardial infarction by the Mantel-Haenszel fixed-effects method and DerSimonian and Laird random-effects method. The odds ratios and 95% CIs for a treatment effect on mortality are shown on a logarithmic scale. The statistical significance reached less than 0.05 in 1973 with the fixed-effects method and in 1977 with the random-effects method. (Redrawn from Lau J, Antman EM, Jimenez-Silva J, et al: Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327:248-54.)

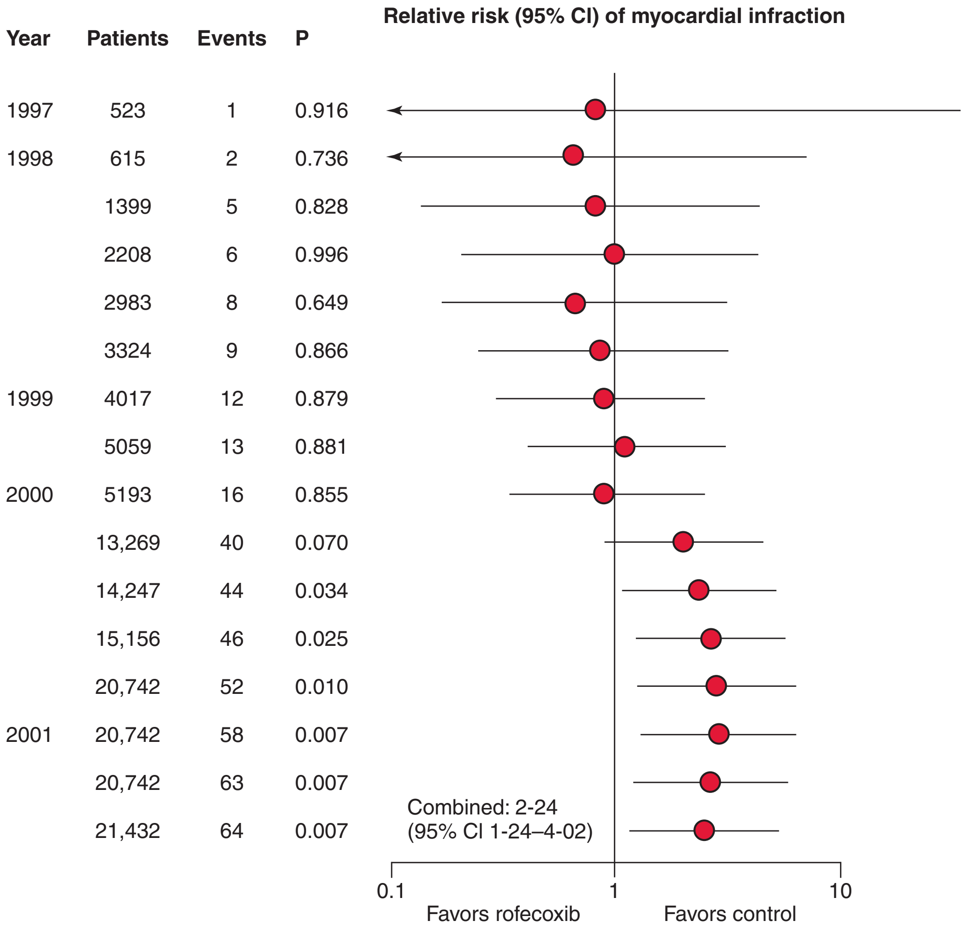


Figure 1–13 Cumulative meta-analysis of 16 randomized clinical trials (RCTs) comparing rofecoxib versus control. An increased risk of myocardial infarction was already evident in 2000 when 14,247 patients had been randomized and a total of 44 events had occurred. Subsequent trials increased the number of patients to 21,432 and the number of events to 64. The confidence intervals were narrowed as subsequent trials were reported but the point estimate still favored control therapy. (Redrawn with permission from Juni P, Nartey L, Reichenbach S, et al: Risk of cardiovascular events and rofecoxib: Cumulative meta-analysis. Lancet 2004;364: 2021-29.)

certain collections of trials of increasing risks of type I error when multiple looks are taken at the accumulating data, more stringent statistical standards for the declaration of significance may be required. One proposal that has been introduced to deal with cumulative meta-analysis is the concept of *optimum information size*, which is defined as the minimum amount of information required in the collective literature to arrive at a reliable conclusion regarding an intervention.[95] Using estimates of event rates and anticipated treatment effects, standard sample size calculations for a randomized trial may be used to determine the cumulative number of patients that must be enrolled in a series of trials to provide the optimum information size. The same interim monitoring techniques used by a DSMB for an individual RCT can be adapted to monitoring evidence as trials are added to a cumulative meta-analysis.[143]

Meta-regression

The majority of meta-analyses in the cardiovascular literature report an average treatment effect estimated from the available studies. To move beyond the current methodology, several investigators have proposed that estimates of the treatment effect be expressed as a function of study-specific features such as years of study, drug dose, characteristics of patients enrolled (e.g., age, gender, race), or average mortality in the control group.[96,97] Adjustments for covariates in clinical trials can be accomplished with the use of regression techniques, and thus the term *meta-regression* has been introduced.[98] Meta-regression is useful for identifying sources of heterogeneity among clinical trials and for establishing clinically important relationships such as dose-response and changes in the incidence of outcome variables (e.g., primary ventricular fibrillation in acute MI) between studies conducted in the distant past and those conducted later.[150]

Future Trends in Meta-analysis

The previous discussion on meta-analysis treats the individual RCT as the unit of analysis. The difference between the aggregate result for the test and control groups for each trial is calculated and then pooled with the observed differences in other trials. Ideally, the individual patients in each trial should be the *unit of analysis* to assess whether the treatment effect is modified by certain patient characteristics. Collaborative efforts of trialists studying antiplatelet therapy for a wide range of cardiovascular conditions, fibrinolytic therapy for suspected MI, and coronary artery bypass surgery (CABG) versus medical therapy for coronary heart disease illustrate the power of pooling individual patient level data to provide estimates of the treatment effect stratified by various clinical profiles (e.g., age, gender, ventricular function, history of infarction or stroke)[78,79,99] (Figs. 1–14 and 1–15). The success of these efforts is likely to inspire other investigators to plan prospectively for pooling of case reports from information across related trials.

Presentation features	Percent of patients dead: Fibrinolytic	Percent of patients dead: Control	Stratified statistics: O–E	Stratified statistics: Variance	Chi-square test of odds ratios in different patient categories: Heterogeneity	Trend
ECG					21.28 on 6 df (*P* < .01)	
BBB	18.7%	23.6%	– 24.5	83.3		
ST elev, anterior	13.2%	16.9%	– 122.0	420.6		
ST elev, interior	7.5%	8.4%	– 27.1	237.4		
ST elev, other	10.6%	13.4%	– 42.1	159.6		
ST depression	15.2%	13.8%	12.9	108.7		
Other abnormality	5.2%	5.8%	– 9.6	103.2		
Normal	3.0%	2.3%	3.4	12.9		
Hours from onset					9.69 on 4 df (*P* <0.05)	9.55 on 1 df (2*P* <0.002)
0–1	9.5%	13.0%	– 29.3	83.3		
2–3	8.2%	10.7%	– 100.2	354.8		
4–6	9.7%	11.5%	– 78.5	387.6		
7–12	11.1%	12.7%	– 51.5	336.7		
13–24	10.0%	10.5%	– 11.1	212.6		
Age (years)					8.27 on 3 df (*P* <0.05)	6.58 on 1 df (2*P* < 0.01)
<55	3.4%	4.6%	– 45.9	155.6		
55–64	7.2%	8.9%	– 86.3	360.0		
65–74	13.5%	16.1%	– 113.7	533.0		
75 +	24.3%	25.3%	– 12.6	266.6		
Gender					1.99 on 1 df (NS)	
Male	8.2%	10.1%	– 208.1	928.0		
Female	14.1%	16.0%	– 62.2	436.8		
Systolic BP (mm Hg)					1.31 on 3 df (NS)	0.68 on 1 df (NS)
<100	28.9%	35.1%	– 38.7	132.2		
100–149	9.6%	11.5%	– 168.9	850.0		
150–174	7.2%	8.7%	– 59.2	290.0		
175 +	7.2%	8.2%	– 10.8	74.1		
Heart rate					0.51 on 2 df (NS)	0.31 on 1 df (NS)
<80	7.2%	8.5%	– 83.2	464.9		
80–99	9.2%	11.3%	– 65.8	287.2		
100 +	17.4%	20.7%	– 51.7	238.6		
Prior MI					2.09 on 1 df (NS)	
Yes	12.5%	14.1%	– 43.7	322.4		
No	8.9%	10.9%	– 228.5	1001.9		
Diabetes					1.57 on 1 df (NS)	
Yes	13.6%	17.3%	– 41.4	145.7		
No	8.7%	10.2%	– 142.6	830.4		
ALL PATIENTS	**2820 / 29,315 9.6%**	**3357 / 29,285 11.5%**	**– 269.5**	**1377.4**		

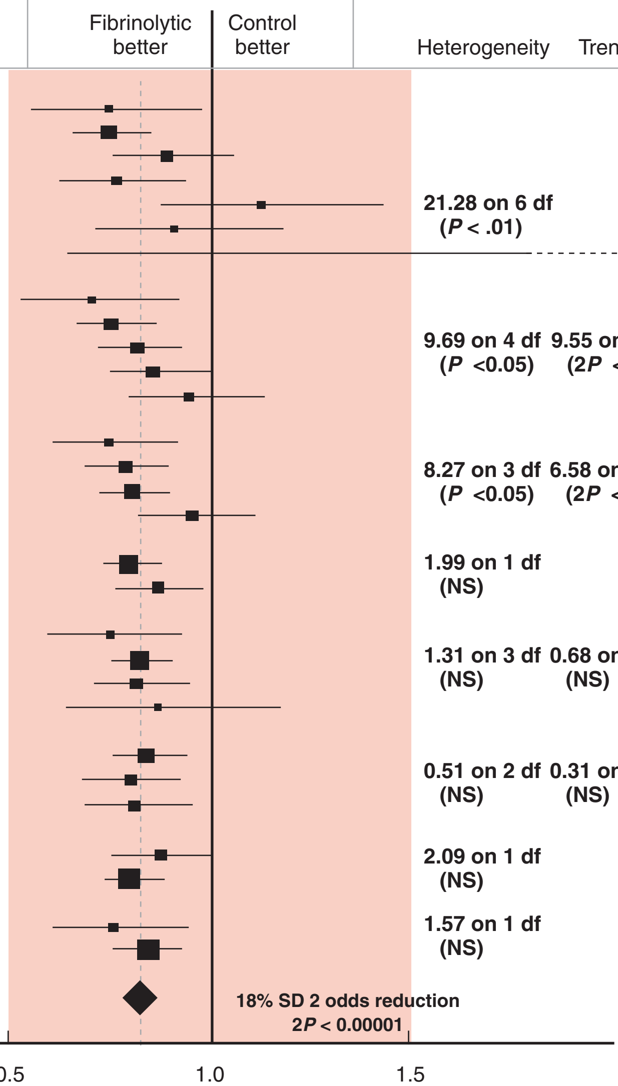


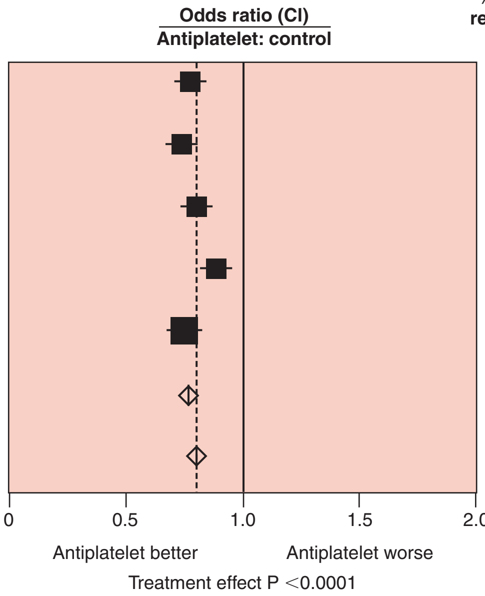
Figure 1–14 Proportional effects of fibrinolytic therapy on mortality during days 0 to 35 subdivided by presentation features. "Observed minus expected" (O-E) number of events among fibrinolytic-allocated patients (and its variance) is given for subdivisions of presentation features, stratified by trial. This is used to calculate odds ratios (ORs) of death among patients allocated to fibrinolytic therapy to those among those allocated control. ORs (filled squares with areas proportional to amount of "statistical information" contributed by the trials) are plotted with their 99% confidence intervals (CIs) (*horizontal lines*). *Squares to left of the solid vertical line*, Benefit (significant at two-tailed $P < 0.01$ only where entire CI is to left of vertical line). Overall result and 95% CI (*represented by diamond*) with overall proportional reduction in the odds of death and statistical significance given alongside. The χ^2 tests for evidence of heterogeneity of, or trends in, the size of ORs in subdivisions of each presentation feature are also given. BP, blood pressure; ECG, electrocardiogram; MI, myocardial infarction. (Redrawn from Fibrinolytic Therapy Trialists' [FTT] Collaborative Group: Indications for fibrinolytic therapy. Lancet 1994;343:311-22.)

How to Read and Interpret a Meta-analysis

A series of practical questions that readers should ask when assessing a meta-analysis are shown in Table 1–6. The same standards should apply whether the physician is reading an overview of a therapeutic modality or the results of a diagnostic test for a medical condition.[100,101] Readers must be convinced that the authors attempted to answer a focused question of clinical importance, that all relevant studies were included, and that an attempt was made to assess the data for evidence of heterogeneity and to explain between-trial variability if it is present. As with individual clinical trial reports, an overview should include a statement of the pooled treatment effect that incorporates both RR reduction and ARD and conveys the information in a clinically practical fashion (e.g., number to treat and number of lives saved per 1000 patients treated).

When attempting to apply the findings of an RCT or overview of multiple RCTs to an individual patient, the clinician

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10,022 (17.0)	−159.8	567.6	25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	−181.5	519.2	30 (4)
Previous stroke/transient ischemic attack	21	2045/11,493 (17.8)	2464/11,527 (21.4)	−152.1	625.8	22 (4)
Acute stroke	7	1670/20,418 (8.2)	1858/20,403 (9.1)	−94.6	795.3	11 (3)
Other high risk	140	1638/20,359 (8.0)	2102/20,543 (10.2)	−222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6035/51,494 (11.7)	7644/51,736 (14.8)	−715.7	2449.6	25 (2)
All trials	**195**	**7705/71,912 (10.7)**	**9502/72,139 (13.2)**	**−810.3**	**3244.9**	**22 (2)**



Heterogeneity of odds reductions between:
5 categories of trial: χ^2=21.4, df=4; P=0.0003
Acute stroke v other: χ^2=18.0, df=1; P=0.00002

Figure 1–15 Proportional effects of antiplatelet therapy on vascular events (myocardial infarction, stroke, or vascular death) in five main high-risk categories. Stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials (*black square*) along with its 99% CI (*horizontal line*). Meta-analysis of results for all trials (and 95% CI) is represented by an *open diamond*. Adjusted control totals have been calculated after converting any unevenly randomized trials to even ones by counting control groups more than once, but other statistical calculations are based on actual numbers from individual trials. (Redrawn with permission from Antithrombotic Trialist's Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.)

must determine whether his or her patient is similar to those enrolled in the trials.[102-104] Although there may be a temptation to focus on subgroup information from the meta-analysis to determine whether a given patient is likely to experience more or less than the average benefit of the treatment, this must be done cautiously.[74] Subgroup analyses are more reliable if there is a highly significant treatment difference, if they represent hypotheses established before trial initiation, if they are consistent across studies, and if they are biologically plausible.[100] The potential risks of the therapeutic intervention should be considered and discussed with the patient to ensure that the treatment decision is consistent with his or her concerns about quality of life.

COST-EFFECTIVENESS ANALYSIS

Cost and *resource allocation* are priorities in the health care agenda of physicians, as well as health care planners, administrators, and economists. Techniques for examining costs in relation to benefit or effectiveness of medical interventions are, therefore, of great importance—especially in the practice of cardiology.[105,106]

Cost-effectiveness analysis (CEA) is the standard for examining cost in relation to benefit. Here, the total cost (*resource impact*) of a treatment in dollars is determined in relation to its effectiveness to determine the "value" of the service. Effectiveness may be expressed in terms of *years of life saved* (YLS) or prolonged, where it is called *CEA*. *Quality-adjusted life years* (QALY) prolonged are also generally called CEA but may be called *cost utility analysis;* or they may be given in terms of the monetary value of life, where the technique is labeled *cost benefit analysis*.[107,108]

As generally applied in CEA, the cost and *life expectancy* (LE) or QALY for one strategy are compared with those of another "competing" strategy. For example, in comparing CABG surgery with medical therapy, one determines the entire cost (including follow-up and future events) and the LE of surgery and then subtracts the cost and the LE of drug therapy.

$$\frac{\Delta\ \text{Cost}}{\Delta\ \text{YLS}} = \frac{\text{Cost}_{\text{CABG}} - \text{Cost}_{\text{med Rx}}}{\text{LE}_{\text{CABG}} - \text{LE}_{\text{med Rx}}}$$

In this way, the *incremental* or *marginal* cost effectiveness (i.e., added cost for added benefit) can be derived.

CEA can be applied to any diagnostic or treatment strategy (although for diagnostic strategies, CEA must take into account resulting treatments as well). At times, only the cost and not the effectiveness (and thus not the "value") of a medical service is determined. This technique is called *cost identification* or *cost minimization analysis*.[107,109]

The usefulness of CEA depends on the ability to compare among health care interventions.[107-111] This may be accomplished by league tables (essentially a rank order list of the cost-effectiveness of a number of medical interventions) or other means (see later). Some authors have introduced a note of skepticism regarding CEA reports because those funded by for-profit organizations are more likely to describe favorable findings with attractive QALY calculations.[112,113]

Table 1–6 How to Read and Interpret a Meta-analysis

Are the Results of the Study Valid?
Primary Guides
Did the overview address a focused clinical question?
Were the criteria used to select articles for inclusion appropriate?
Secondary Guides
Is it unlikely that important, relevant studies were missed?
Was the validity of the included studies appraised?
Were the assessments of studies reproducible?
Were the results similar from study to study?
What Are the Results?
What are the overall results of the review?
How precise were the results?
Will the Results Help Me in Caring for My Patients?
Can the results be applied to my patient care?
Were all clinically important outcomes considered?
Are the benefits worth the harms and costs?

Reproduced from Oxman A, Cook D, Guyatt G, et al: Users' Guides to the Medical Literature.VI. How to use an overview. JAMA 1994;272:1367-75.

Components of Cost-Effectiveness Analysis

Cost

Cost determination is complex, and there has been less than perfect consistency among analyses, which can be greatly influenced by the cost accounting method used.[97-111,114] *Actual cost* is defined as the value of services incurred by the provider of care. Charges are "prices" for services. Payments are the monies paid to providers for services.

Actual costs are divided into *direct* and *indirect costs*. Direct costs are the direct organizing and operating expenditures in the delivery of care, and they may be medical (e.g., provider services, hospitalization, drugs, devices, and so on) or nonmedical (e.g., food, transportation, and housekeeping).[115,116] *Indirect* cost in health economic parlance may refer to one of two concepts. In hospital parlance, indirect costs refer to *overhead* costs such as for food, mortgage, and so on, and are roughly equivalent to *direct, nonmedical costs*. In other parlance, indirect costs refer to those resulting from loss of income due to illness or death (labor and productivity issues) and can be prodigious for heart disease.[107-111,114,115]

Pain, grief, and suffering related to illness are called *intangible costs*. Although included in CEAs, intangible costs may be part of the denominator in cost-benefit analysis (see later).[117] *Fixed costs* do not vary within a certain time period, usually 1 year (e.g., mortgages, depreciation, and so on). *Variable costs* are those directly applied to services (e.g., laboratory tests, nursing, billing, surgical supplies).[116]

Average (or *unit*) *costs* are total costs divided by total units, whereas *incremental costs* are those incurred by adding one additional unit of service, such as a program or an option. For example, the hospital costs for 1000 cardiac catheterizations may be $1.5 million or $1,500 *average* per case. If the capacity is high and the schedule has openings, the incremental cost of adding 50 *elective* catheterizations might be relatively little—mainly the cost of supplies. On the other hand, in a full schedule, the incremental cost for elective catheterization would involve overtime payments and other extra operating costs.

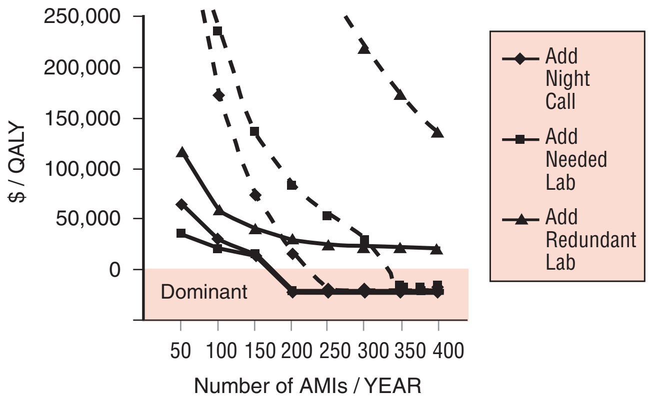


Figure 1–16 Costs/quality-adjusted life year (QALY) of primary percutaneous transluminal coronary angioplasty (PTCA) versus thrombolysis in acute myocardial infarction (AMI), demonstrating the effect of adding emergency hospital services, hospital volume, and differences with the use of randomized clinical trials (RCTs) (efficacy) versus community-based observational (effectiveness) data assumptions. *Horizontal axis*, number of AMIs per year at the admitting hospital (volume); *vertical axis*, cost effectiveness ($/QALY). In the base case in this analysis, the hospital had 200 discharges for AMIs; an existing cardiac catheterization laboratory that performed elective procedures during weekdays; surgical backup; two technical staff members on night call; primary angioplasty offered 24 hours a day/7 days a week; and RCTs were used to derive outcomes (efficacy). *Solid lines*, cost/QALY with "efficacy" assumptions derived from RCTs; *dashed lines*, results estimated from community-based observation data ("effectiveness"). At base case, primary PTCA is dominant. *Diamonds*, results of adding night call; *squares*, added needed laboratory (for both elective and primary PTCAs); *triangles*, added redundant laboratory (for primary PTCA only). Note that with any assumptions, the incremental costs of services can be great, especially where hospital volume is small. Regarding use of RCT or community data (*solid versus dashed lines*), there was little impact on the addition of needed laboratory or night call with high hospital volume (primary PTCA is dominant in both instances), but as AMI volume moves below 200 per year, the impact is much more profound. (Adapted from Lieu TA, Gurly RJ, Lundstrom RJ, et al: Projected cost-effectiveness of primary angioplasty for acute myocardial infarction [with update to 1997 dollars and assumptions regarding dominance maintained]. J Am Coll Cardiol 1997;30:1741-50.)

The impact on cost effectiveness of adding capacity for service is shown in Figure 1–16. Cost per QALY is plotted against the number of baseline acute MIs per year in a particular hospital. The capacity to perform primary percutaneous transluminal coronary angioplasty (PTCA) requires night call

and the potential for a rapid phase-in of a "needed" or "redundant" extra cardiac catheterization laboratory.[118] The incremental cost for adding these additional services is reflected in the less favorable cost per QALY, which rises markedly as the annual acute MI volume falls. Figure 1–16 also compares use of RCT with community-based observational data (see later).

The above distinctions are important in analyzing cost-cutting measures. For example, a decision not to perform a procedure would realize a much lower cost savings in the setting of unused capacity than if one had to add personnel or open up a new procedure room. In Figure 1–15, the markedly less favorable cost effectiveness of emergency primary angioplasty with lower hospital volume has implications for determining which hospitals can efficiently offer this service and for regionalization of services.[119] Such direct policy implications on resource allocation can give CEA political overtones in many situations.

Charges and Payments

The use of charges represents a simplified approach.[120] Charges for physician services in the United States are set well above any reimbursement level so as to assure reimbursement at all levels of payment. In CEAs, it has been common to determine charges and then derive costs based on cost/charge ratios using the Medicare Cost Report. Payments (e.g., Medicare reimbursements) have also been used in analyses.[121]

Resource Consumption

The two steps in determining the overall costs of a medical intervention are to determine the cost of each item (*unit*) and how often each item (unit) is used (*resource consumption*). This includes recurring events such as routine tests, visits, hospitalizations, and others. For example, resource consumption for an implantable cardioverter-defibrillator would include the initial hospitalization, the number of visits required for diagnostic testing, frequency of exercise and other tests, laboratory tests, and the risk of complications and consequent interventions.[122] The cost of each item would then be multiplied by the number thus derived to arrive at overall cost. Resource consumption data are derived from RCTs and data bases[122-125] when possible, but often expert opinion[126,127] is used.

Effectiveness

The most direct index of effectiveness is prolongation of life, expressed as YLS. Some analyses have used the number of lives saved.[128] In addition, because combined endpoints are frequently used in RCTs, cost per *event-free year* has been[129] applied. LE data may come from individual RCTs, meta-analyses of trials, or historical and case-control studies.[123,130-133] RCTs provide only relatively short-term data for LE, generally 2 to 5 years (although some RCTs now have longer term data, e.g., 10 to 12 years,[134] whereas the time horizons of CEAs are usually lifetime. To complete this time horizon, one must merge treatment efficacy coefficients from randomized trials or data bases with natural history studies (the Framingham trial is frequently used),[135] population-based life tables and U.S. Vital Statistics—methodology that addresses different population sets for each component.

Figure 1–17 illustrates the effect of changing the duration of benefit on the results of CEA. Here an analysis was performed on 6 RCTs of prophylactic implantation of the implantable cardioverter-defibrillator (ICD) in which the device was found to prolong life. The horizontal axis is time of benefit and the vertical axis is cost/QALY. In Figure 1–17A, it was assumed that the ICD conferred no additional benefit after the specified time on the horizontal axis; lifetime costs were included and survival curves were assumed to be parallel after the time period. In Figure 1–17B, it was assumed that neither costs nor benefits were incurred after the specified time period. Note the degree of improvement in cost-effectiveness as the time of benefit increases in duration as well as overall differences in results for the two approaches.[136]

The other major measure of effectiveness, the QALY, used in the denominator of CEA attempts to merge LE and health-related quality of life (HRQL). Specifically, the QALY is a downward adjustment in the value of a healthy year as a result of poor health factors (pain, disability, and so on) in the eyes of the patient. It is LE multiplied by a fraction, termed the *utility*, or *quality adjustment coefficient*, which represents the decline in quality of life caused by less-than-perfect health. For example, in a study of CABG surgery, the utility of angina pectoris was considered to be 0.7 with severe angina and 0.9 with mild angina.[137] These utility numbers are multiplied by LE to arrive at the QALY

$$\text{QALY} = \text{U} \cdot \text{LE}$$

where QALY is quality-adjusted life year, U is utility (in each health state), and LE is LE in years (from each health state). Therefore, 1 year of life rated as 70% of perfect health (U = 0.7) would have a QALY of 0.7, and 2 years would have a QALY of 1.4. This value is then put into the following formula:

$$\frac{\Delta\ \text{Cost}}{\Delta\ \text{QALY}} = \frac{\text{Cost}_{\text{new Rx}} - \text{Cost}_{\text{competing Rx}}}{\text{QALY}_{\text{new Rx}} - \text{QALY}_{\text{competing Rx}}}$$

A favored method of obtaining utilities is the *time tradeoff*.[138-141] An individual is asked what LE in perfect health would be equivalent to a longer LE with a health problem. If the individual considers that 1 year living with a given degree of angina is equivalent to 9 months in perfect health, then the utility is 0.75; for 8 months, it is 0.6, and for 6 months, it is 0.50. States felt to be worse than death have also been addressed.[142] *Standard gamble* assesses what one would gamble for a given beneficial option. For example, what mortality risk might one accept in CABG surgery for its benefit?[143] (Fig. 1–18). In other instances, short-term quality-of-life adjustments are made for transient incapacitation by a subtraction method (e.g., the amount of time in the hospital for a stroke might be subtracted from a "healthy year"). QALYs may be expressed as patient or community preference.[115-117]

An important issue no matter how QALYs are evaluated is their fundamentally subjective nature. For example, the subjective worth of a specific health state might be rated differently by individuals at different times. It might vary based on many other factors such as whether the anticipated state is one involving health improvement or decline, and the exact prognosis without treatment. One may also view things differently when asked hypothetically about a life-prolonging treatment

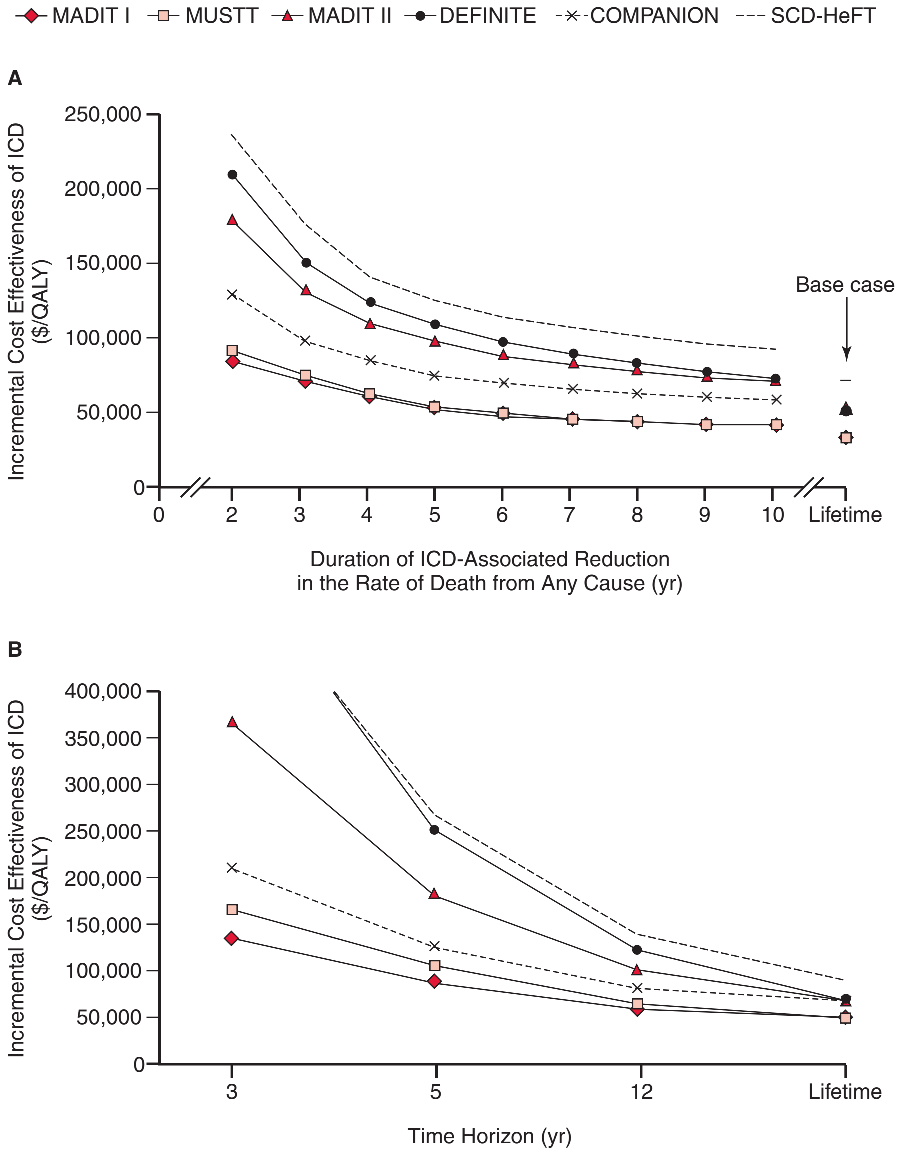


Figure 1–17 Variation in the incremental cost effectiveness of prophylactic implantation of an implantable cardioverter defibrillator (ICD) with changes in the time horizon of ICD effectiveness in preventing sudden death. Shown are results from six trials in which the ICD was found to be efficacious (Multicenter Automatic Defibrillator Implantation Trial I [MADIT I]; MADIT II; the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation [DEFINITE] trial; the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [COMPANION] trial; the Multicenter Unsustained Tachycardia Trial [MUSTT]; and the Sudden Cardiac Death in Heart Failure Trial [SCD-HeFT]. (See symbols at top of figure for identification of trials from which data are posted). The *x*-axis shows duration of ICD-related reduction in mortality after which there is no benefit and the *y*-axis shows cost effectiveness. **A,** lifetime costs that were included in survival curves were assumed to be parallel after the time period. In this analysis, the costs for both treatment strategies continue through the patient's projected lifetime. The base-case assumption is that the benefit lasts a lifetime (*arrow*). **B,** both costs and benefits are assumed to stop at the specified time. QALY, quality-adjusted life-year. (Redrawn from Sanders GD, Hlatky MA, Owens DK: Cost-effectiveness of implantable cardioverter defibrillators. N Engl J Med 2005;353:1471-80.)

than when one is actually in the situation. Further exploration of potential background modifiers such as percentage increase in life years or percentage increase in QALYs have been suggested and might be considered appropriate in some cases.[144]

Cost-Benefit Analysis

Although cost-benefit analysis is favored by many economists, it is the least used method by health economics analysts. Here the numerator is cost, as in CEA, but the denominator is expressed in the dollar value of medical benefits.[115,145] There are obvious difficulties in this form of expression, especially for physicians. A formula for cost-benefit analysis is as follows:

$$\frac{\Delta \text{ Cost}}{\Delta \text{ Benefit}} = \frac{\$10{,}000}{\$2{,}000}$$

$$\text{Net Cost} = \Delta \text{ Cost} - \Delta \text{ Benefit} = \$10{,}000 - \$2{,}000 = \$8{,}000$$

A $\Delta C/\Delta B$ of 1 with a consequent net cost of 0 might be considered desirable.

Decision Analysis

CEA requires a method of organizing the cost and effectiveness components of a medical strategy in a precise manner to enable the quantification of outcomes and assignment of costs. The method used is *decision analysis*.[146-148]

In decision analysis,[149] a complex situation is distilled into all of its smaller components and organized in a *decision tree*. The decision tree maps out how populations move through various disease states and displays the diagnostic and therapeutic strategies, the probabilities and consequences of each strategy, and in the case of CEA, the costs. In this construct, the *Markov model* has been used to consider changes in state or *transitions* of a population as it moves through a disease process (e.g., from health to acute MI to recovery).[146,148,150]

Figure 1–19 is a decision tree of the CEA of coronary artery disease (CAD) preventive treatment in high-risk (A) and low-risk (B) patients. It is a highly simplified tree based on a previously published hypothetical example.[151] In the tree, there are two types of branch points:

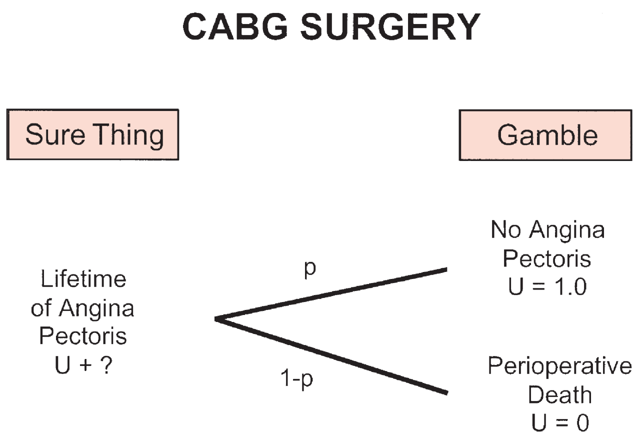


Figure 1–18 Standard gamble of J Von Neumann and O Morganstern (Theory of Games and Economic Behavior. Princeton, NJ: Princeton University, 1944) showing two choices. *Left*, The choice (sure thing) represents a lifetime with the disease, such as coronary artery disease. *Right*, Choice is a gamble to perform coronary artery bypass graft (CABG) surgery with two probabilities: that the patient will return to normal health (p) (*top*) or there will be a perioperative death (1-p) (*bottom*). One varies (p) until the indifference probability, which represents the utility, is reached. For example, if the subject cannot choose between living with angina and an 80% chance of perfect health versus a 20% chance of immediate death, the utility (U) is 0.8. (Redrawn from Kupersmith J, Holmes-Rovner M, Hogan A, et al: Cost-effectiveness analysis in heart disease, Part 1: General principles. Progr Cardiovasc Dis 1994;37:161-84.)

1. *Decision nodes* (squares)—branch point where a decision has to be made—in this case, the decision is *to* use or *not to* use a CAD-preventive regimen;
2. *Chance nodes* (circles)—branch point where one of several states or events may occur that are beyond the decision maker's control. Occurrences here include death, acute MI, other disease states, and alive and well.

Every occurrence (i.e., every limb at a chance node) is assigned a probability. In Figure 1–20A, the probability that a high-risk patient receiving preventive therapy dies in 1 year is 0.05 versus 0.10 in patients not receiving the therapy; for low-risk patients (see Fig. 1–20B), the corresponding values are 0.005 and 0.010. (Other assumptions are noted in the figure legend.) Each limb is also assigned a cost ($2,000 for preventive therapy, $20,000 for CABG, and so on.). The sum total of all probabilities and costs then forms the CEA formula. Results in this hypothetical example are that the cost effectiveness of preventive therapy is $12,800/YLS in high-risk patients and at a much less favorable $216,900/YLS in low-risk patients. This 17-fold more favorable cost effectiveness in the high-risk group results from the higher mortality rates (with an attendant greater gain in effectiveness). In addition, because of high morbidity rates at high risk, expensive interventions and surgical procedures are more common, leading to more substantial monetary gain from the aversion of such interventions and procedures, as in the case of enoxaparin, which is dominant in acute coronary syndrome patients.[125]

Limbs of the tree become much more complex than shown in Figure 1–19 as one elaborates on all the nuances of diagnosis and care, although it is difficult to include every last nuance. There are generally simplifying assumptions[152,153] and there may also be components of intuitive thinking that are not captured by decision analysis. For example, one nuance might be that not only will there be fewer acute MIs with preventive treatment but also the MIs will be less severe. The tree must also be compact and understandable[154] and a given nuance may have little impact on the overall results (or be addressed by sensitivity analysis)(see later).

Decision analysis models have been compared with the recommendations of expert clinicians. In one study, QALY gain and cost/QALY were compared with appropriateness scores developed by an expert panel on whether or not to undertake post-discharge coronary angiography within 12 weeks after MI. There was a significant correlation between expert-opined appropriateness of angiography and both QALY gain (Spearman rank correlation coefficient, 0.58, $P < 0.001$) and cost effectiveness (-0.66, $P < 0.001$). No indications that clinicians deemed appropriate were valued at more than $50,000/QALY, whereas clinicians were more conservative than the decision analysis model in certain asymptomatic patients (i.e., intervention considered inappropriate but valued at less than $50,000/YLS).[155]

Sensitivity Analysis

Because of the spectrum of data used in CEA , there is often uncertainty, and to address this uncertainty, one uses *sensitivity analysis*. Here, one varies the assumptions made in the base case on specific aspects of the analysis and then repeats the calculation. One asks the question "What if" and then determines whether results were critically dependent on the assumption.[107,156] Figures 1–20 through 1–23 show a series of *one-way* sensitivity analyses (i.e., testing of only one assumption) based on the data in the decision tree shown in Figure 1–19. Figure 1–24 is a two-way sensitivity analysis.

Figure 1–20 shows the effects of varying the cost of preventive therapy in high-risk (A) and low-risk (B) situations. The cost-effectiveness results are linearly related to the cost of prevention and *sensitive* to it; that is, cost effectiveness varies greatly as the cost of prevention changes. Of interest is that the "break-even" threshold of prevention is the cost at which cost savings of prevention (e.g., reduction of CABG, PTCA, acute MI, and so on) in totality equals the costs of prevention. This is lower in the high-risk situation, $108 versus $913. The other value of interest is what the cost of prevention would have to be in the low-risk situation for it to be "cost effective," $50,000/YLS (in this example)—in this case, $544.

Figure 1–21 shows the effect of changing the percent mortality benefit in high-risk (A) and low-risk (B) situations. At base case, the mortality benefit was assumed to be 50%. The "cost effective" threshold ($50,000/YLS) for high risk is a mortality benefit of only 11.3%, whereas for low-risk situations, cost effectiveness is still $121,000/YLS at a mortality benefit of 90%. Figure 1–22 shows the sensitivity of changing the assumptions related to the cost of CABG (A), PTCA (B), and acute MI (C). Cost effectiveness is improved (i.e., at a lower value) as the costs of these eventualities rise and there are more savings from averting them, but the model is relatively insensitive to the changes in these costs. Figure 1–23 shows the

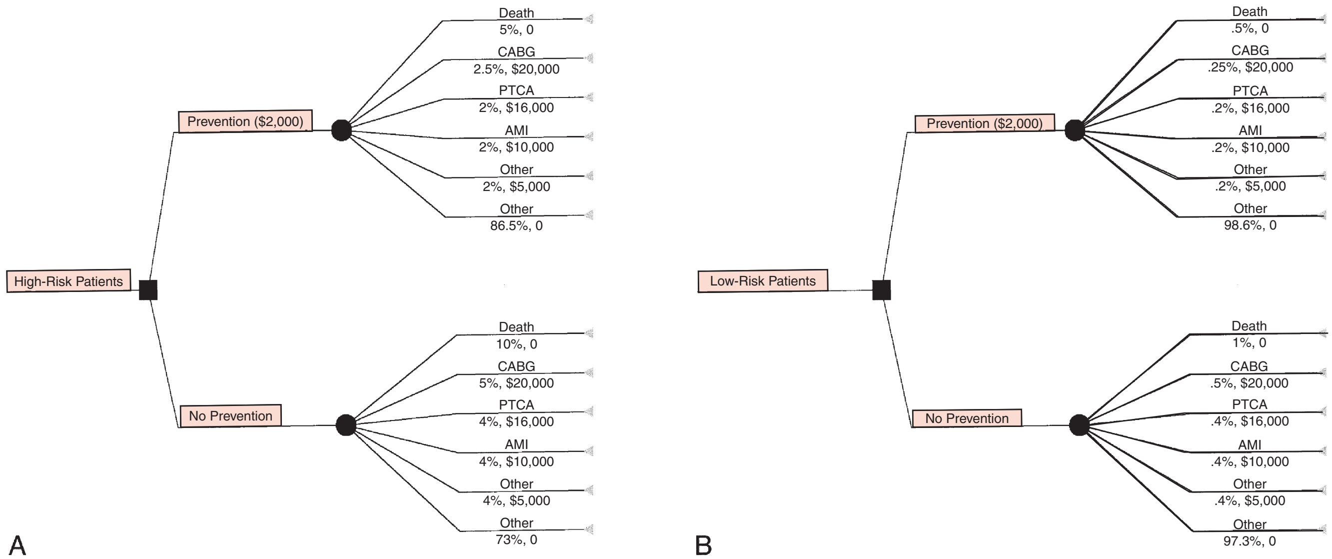


Figure 1–19 Decision trees of cost effectiveness (cost/years of life saved [YLS]) of preventive therapy for coronary artery disease in high-risk (**A**) and low-risk(**B**) patients. Decision trees are hypothetical for explanation purposes only and not based on derived data. Prevention is assumed to cost $2,000. Decision nodes (*filled square*) are whether or not to use preventive therapy. Chance nodes (*filled circles*) show occurrences of death, coronary artery bypass graft surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA), acute myocardial infarction (AMI), other disease states, and alive and well with percentages and long-term costs of each. In this example, diagnostic tests are considered within the overall cost of preventive therapy, as are any other events and treatments that an individual might have received, such as complications of CABG, AMI, and so on. Time horizon is 6 years, there is no discounting, all patients are assumed to die at mid-year, numbers are annual figures and preventive therapy is assumed to reduce death and events by 50%. Cost effectiveness is $12,800/YLS in high-risk and $216,000/YLS in low-risk groups. (Basic concept from Goldman L, Garber AM, Grover SA, Hlatky MA: Task force six, cost-effectiveness of assessment and management of risk factors. J Am Coll Cardiol 1996;27:964-1097, with modifications.)

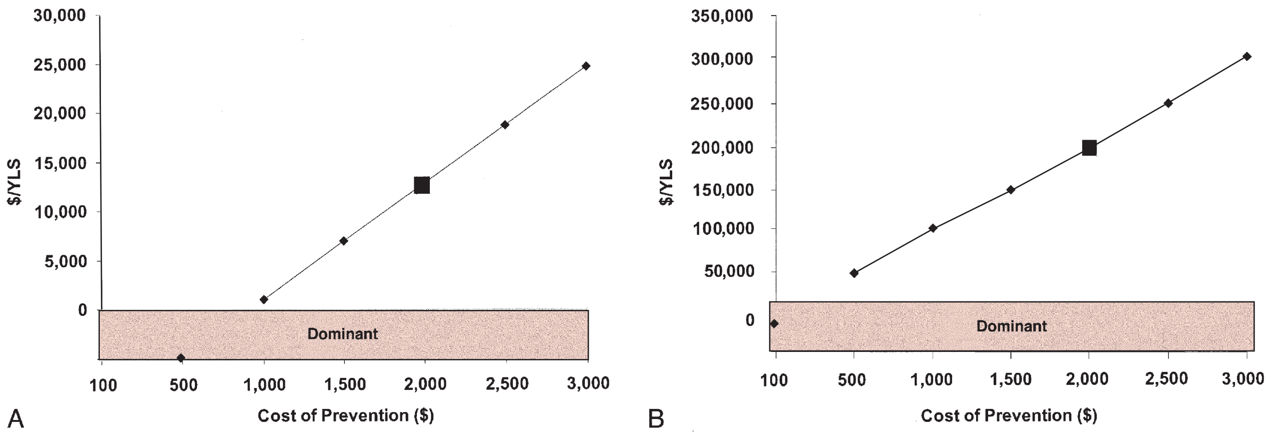


Figure 1–20 Sensitivity analysis showing effects of varying cost assumptions of preventive therapy on cost effectiveness in high-risk (**A**) and low-risk (**B**) populations shown in Figure 1–19. At base case (*filled square*), the cost is $2,000. Cost effectiveness varies greatly and linearly with the cost of preventive therapy (i.e., cost effectiveness is sensitive to changes in cost of prevention). The cost threshold where prevention becomes dominant (i.e., the "break-even" point is $108 in high-risk and $913 in low-risk patients). The threshold cost for preventive therapy being "cost effective" (i.e., $50,000/YLS) at low risk is $544. Note differences in vertical scales in **A** and **B.**

results of changing assumptions regarding the mortality in the "no-prevention" population without changing the proportional mortality benefit of prevention. At base case, mortality rate in the no-prevention population was assumed to be 5% in the high- and 0.5% in the low-risk situations. The threshold for a cost-effective intervention ($50,000/YLS) is 1.9% population mortality rate. This number could be interesting for policy makers to decide which populations should have such interventions (e.g., in a primary prevention study).

Figure 1–24 is a *two-way sensitivity analysis* in which the assumptions both on costs of prevention and on mortality in the no-prevention group are varied. Here, one can elaborate zones of dominance, favorable cost effectiveness, and so on. In Figure 1–24, there is a zone of dominance (to the right of

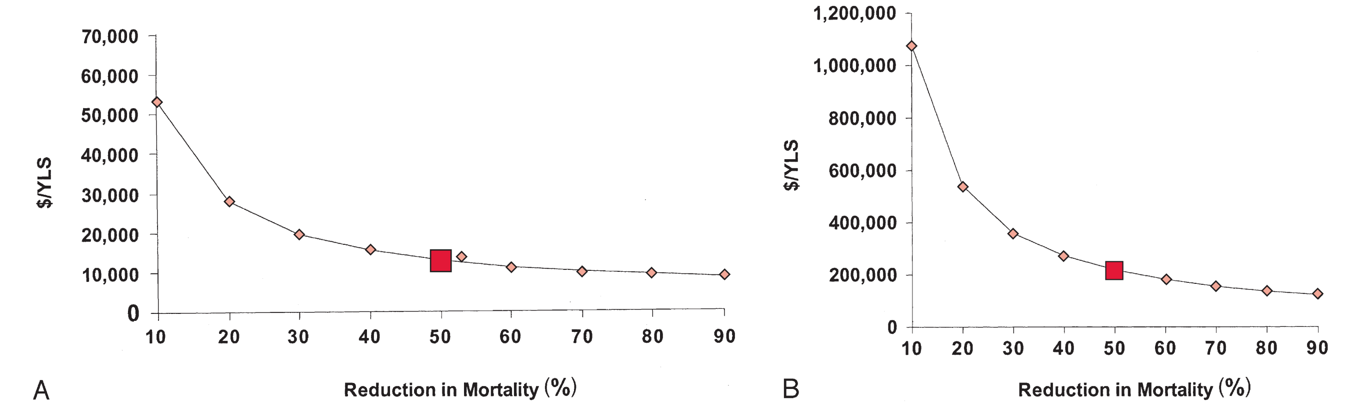
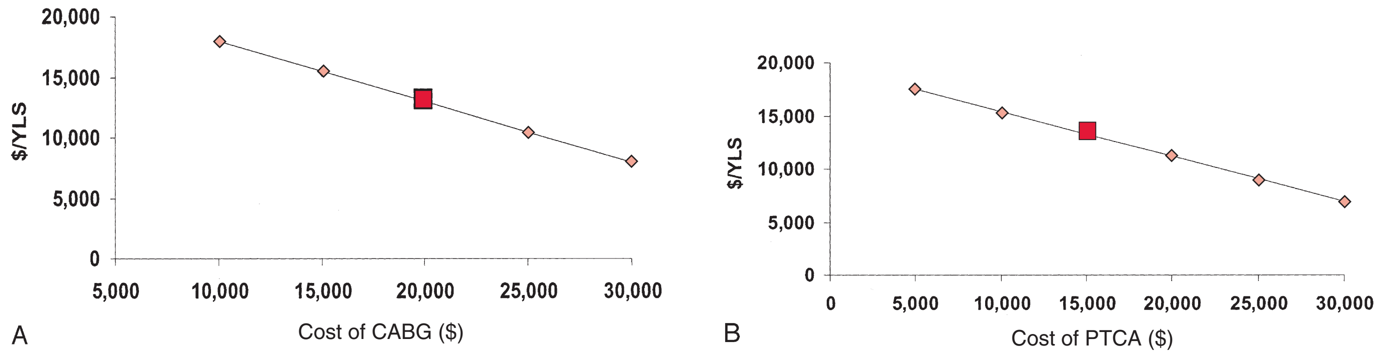


Figure 1–21 Sensitivity analysis of altering benefit assumptions (% reduction in mortality) of preventive therapy in high-risk (**A**) and low-risk (**B**) populations shown in Figure 1–19. Base case benefit is a mortality reduction of 50% (*larger square*). Cost effectiveness changes in both instances become more profound as one moves to a mortality benefit <30%. Of particular interest is that the threshold level for the intervention being "cost effective" (<$50,000) in high-risk populations is still a very modest mortality gain, 11.3%. However, in low-risk situations, even at a mortality benefit of 90%, cost effectiveness is still $121,000/YLS (years of life saved).



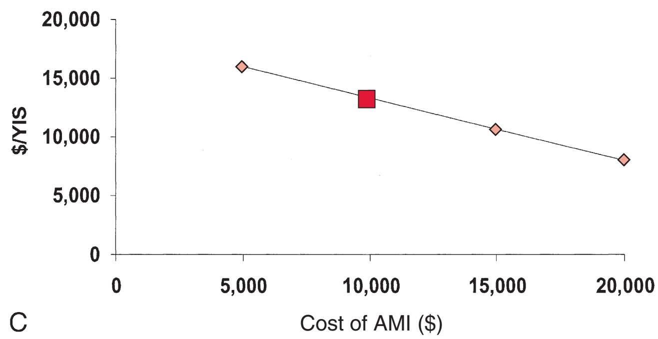


Figure 1–22 Sensitivity analysis of varying cost assumptions of coronary artery bypass graft surgery (CABG; **A**), percutaneous transluminal coronary angioplasty (PTCA; **B**), and acute myocardial infarction (AMI; **C**) in high-risk populations shown in Figure 1–19 (*filled squares* show base case). Cost effectiveness is relatively insensitive to these changes (i.e., still favorable even with a wide range of assumptions).

break even), a cost-effective zone (between break even and $50,000/YLS), and a zone where there is less favorable cost effectiveness (to the left of $50,000/YLS). *Three-way sensitivity analysis* can also be performed.[157]

Statistical Analysis

Traditional statistical analysis, and therefore meaning of a particular result, is probably less well developed for CEA than for other types of study, such as RCTs. Confidence interval determination is now a more frequent component of CEA.[69,158,159] Nonparametric bootstrap analysis is commonly used.[160,161]

Longevity Cost Inclusions

If a medical intervention prolongs life, there is added cost. In analyses of CABG, for example, one uniformly includes costs related to CAD during the extended life period. However, other diseases, such as cancer, may also occur and there is dispute as to inclusion of these particular costs, although they do not change the results much.

Perspective

Perspective reflects who pays the bill or who may receive benefits from efficiencies. *Payers* may include hospitals, health

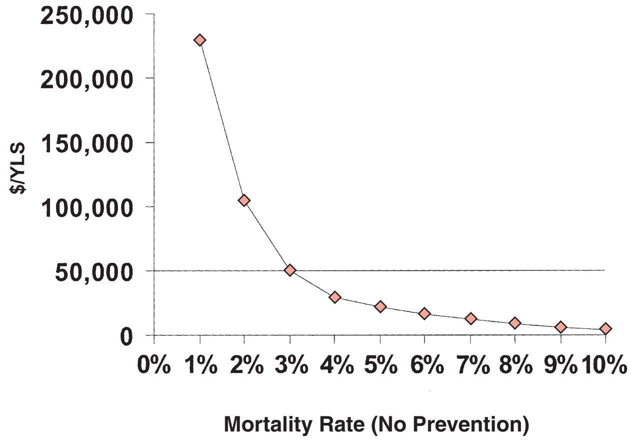


Figure 1–23 Sensitivity analysis of assumptions regarding the mortality rate in the no-prevention population in Figure 1–19 with mortality benefit assumed to remain at 50%. At base case, mortality was assumed to be 5% in the high-risk and 0.5% in the low-risk groups. Threshold for "cost-effective intervention" ($50,000/years of life saved [YLS]) is a mortality in the no-prevention population of 1.9%.

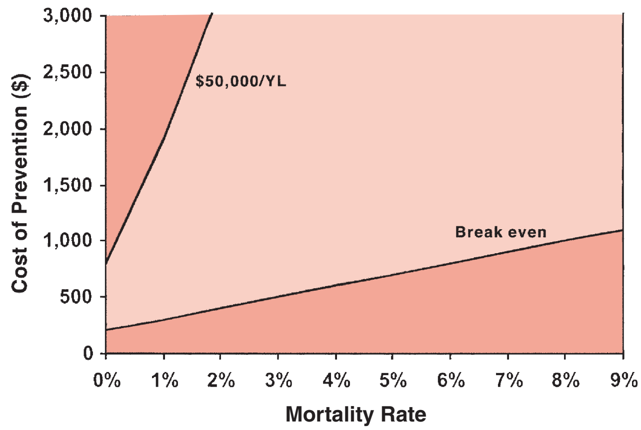


Figure 1–24 Two-way sensitivity analysis showing effects of both cost of preventive therapy and death in the low-risk population group of population shown in Figure 1–19. Shown are identity lines for "break even" and a cost effectiveness of $50,000/years of life saved (YLS).

maintenance organizations, providers, patients, or society as a whole. At times, perspectives may clash. For example, a shortened hospital length of stay of a patient benefits the hospital because payments from insurance companies are prospective (via diagnosis-related groups) (DRGs) and similar regardless of the length of stay. For the patient, it may be economical to stay in the hospital because there are many out-of-pocket costs to avoid, including possible home care. From a societal perspective, the sum of hospital and long-term outpatient costs should be considered.[162,163] As can be seen, each entity may view costs from the perspective of its own particular "silo" and the general welfare may be a lesser consideration. It is recommended that societal perspective be the standard for analyses, in part to ensure comparability.[164] However, an individual entity (hospital, health care plan, and so on) may find CEA very useful in making rational allocations of resources from its own perspective.

Discounting

Discounting is a method to equalize present and future costs.[107,115,146,155] In both economics and life, future benefits and adversities are not valued the same as those of the present. For example, we would rather die in the future. In another example, technologic enhancement for the treatment of coronary artery disease may be both more possible and cheaper in the future, devaluing the role of cholesterol lowering. Therefore, money spent "now" for benefits is worth more than money spent in the future. The method used for equalizing time is *discounting* of both future costs and effectiveness. A 3% per year discount of future items is recommended (a reflection of average yield in public investments), although many past analyses have used 5% per year.

Because the timing of cost and benefits of a particular intervention varies, the impact of discounting also varies. In the case of long-term drug treatment (e.g., for hypertension) costs are relatively uniform over time (e.g., drug costs, intermittent diagnostic testing, complications) and benefits are delayed. For surgical or procedural interventions, there is a large initial and much more modest long-term cost, and benefit starts immediately. Here, one gets a return over time for the initial investment. The overall cost effectiveness of these two types of medical interventions may be comparable, but a higher discount rate has more of an impact in devaluing the benefits of prevention because these benefits are more in the future.

Subgroup Analysis

Analyses may be targeted on the basis of risk (see Fig. 1–19) but also to specific subgroups, such as women,[152] minorities, and different age groups. For age, the interaction is complex. In elderly persons, there is higher risk (associated with more favorable cost effectiveness of an intervention) and shortened LE and tendency toward lower efficacy coefficients (both associated with less favorable cost effectiveness).

Generalizability of Data

Although issues related to reliability of the data applied to CEAs are in part addressed by sensitivity analysis, some remain. One of the most important issues is generalizability of data to the particular clinical situation under analysis. For example, population cohorts that form the basis of a particular CEA may have individual peculiarities in disease severity, approaches to quality, medical care, income, perceptions, ethnicity, geography, domicile of origin, and the nature and size of the local health care delivery system—all influential issues on both the cost and effectiveness sides. Styles of practice may also vary, especially for interventional procedures, among individual physicians[165,166] and in different regions of the country.[167]

Costs may also be site or regional specific. Although the medical marketplace has created some site uniformity, there remain large site and regional differences depending on the degree of managed care penetration, negotiating leverage, purchasing power, competition among physicians, and special nature of academic institutions. One approach to address

these differences is *microanalytic modification of costs* that are setting specific.

Efficacy Versus Effectiveness

An important distinction related to generalizability is that between *efficacy* and *effectiveness* data. The population cohort of the typical RCT may have nonrepresentative characteristics, such as high compliance to medication, possibly greater disease severity, limited comorbidity, narrow demography, possible incentives in entering the trial, and others, that may set it apart from the general population (selection bias). This type of RCT determines an ideal *efficacy*, that is, what the intervention "can do." The CEA is a broader study than the RCT and requires *effectiveness*, i.e., what the intervention "will do" in broad populations where compliance is variable, demography is varied, and comorbidity is common. Megatrials such as Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO)[146] overcome some of these problems, but case selection at the individual sites can still skew the study population to some degree. Increasing interest is developing in the concept of pragmatic clinical trials[168] in which every effort is made to answer the effectiveness question in the context of randomization. The goal is to enroll a diverse study population in a comparison of clinically relevant alternatives that measure a broad range of health outcomes.

An example of the possible differences in results between CEAs based on efficacy and effectiveness data is shown in Figure 1–16.[118] Here a sensitivity analysis is used to contrast results from data derived from an RCT (efficacy) with those estimated from community-based observational data (effectiveness) in a CEA of primary angioplasty in acute MI. Of interest is the less favorable cost effectiveness when results are based on community-derived observational data in situations where stresses have to be added to the system to perform primary angioplasty (e.g., adding night call or an additional redundant or needed laboratory [where the lesser efficiency emerges only as the volume of acute MIs declines]).[118] Although in Figure 1–16 the differences in results between RCT and community-based data depend on volume , in other instances, it may be apparent in all situations.

Bias

With all of the these considerations regarding data and because CEA often occurs away from the safe harbor of the RCT, the issue of bias[169] has arisen especially in relation to selection bias and fairness regarding items not captured in the analysis. In constructing the analysis, what costs are included? Which data base is used for effectiveness? Key assumptions, judgments, and constraints that drive recommendations must be explicit and transparent.[170] What are the implicit and explicit budget constraints, and is the analysis transparent on this and other issues?[171] It is important to be vigilant in these areas, especially because the analysis may ultimately guide or even determine policy and may benefit the entity undertaking the analysis.

Standardization of Cost-Effectiveness Analyses

As indicated earlier, the basic purpose of CEA is to compare medical interventions and to do this, one must first address the issues raised above regarding generalizability, bias, cost analysis, and so on. One then needs standardization of technique. Because the methodology used in CEAs has varied, the U.S. Public Health Service in 1996 convened a panel on cost effectiveness and health in medicine to recommend a standardized approach.[108,164,172,173] They recommended that in all CEAs, there should be a *reference case* analysis that incorporates in its methodology the specific individual recommendations of the panel and is available for comparisons with other analyses. In the reference case, one should use societal perspective, CPI inflation-adjusted costs, indirect as well as direct costs, a 3% discount (but also provide sensitivity analysis for 5%), confidence intervals, and community preference QALYs. Inclusion of costs for unrelated diseases in years of extended life is optional.

Evidence suggests that the 1996 report of the U.S. Panel on Cost-Effectiveness in Health and Medicine had some impact on practice.[174] The use of cost effectiveness and related economic analysis techniques has improved and expanded over the past few years, as have efforts to synthesize and interpret results systematically. The United States Preventive Services Task Force (USPSTF), convened in 1998, built on the recommendations of the panel and two prior USPSTF Task Forces, to enhance recommendations intended for the general primary care situation by

1. Proposing a systematic approach for rating the quality of evidence; rating internal validity of each study as good, fair, or poor, based on explicit criteria; using expert stakeholders (topic team) to rate as good, fair, or poor, aggregate internal validity, external validity, and coherence/consistency of the *body* of evidence, weighting studies based on quality and explaining rationale with brief narratives; considering magnitude (effect size) separately from evidence quality but using both issues in making overall recommendations
2. *When quality of evidence is judged to be good or fair*, calculating net benefit (benefits minus harms of a service)
3. Considering benefit from both the individual and population perspectives and preparing outcomes tables that display both outcome frequency and degree of certainty about the information
4. Where possible, considering total economic costs that result from providing a service, both to individuals and to society.[175]

Evidence-based practice centers are using this approach to incorporate information about cost effectiveness into their evidence syntheses.[176] Each analysis considered should be prepared according to current guidelines, and the perspective, time line, and uncertainty around estimates should be openly and clearly stated.[177]

Vehicles for Making Comparisons—League Tables and Thresholds

Ordinarily one compares medical interventions in a *league table* which, as indicated earlier, is a rank order list of the cost effectiveness of a number of medical interventions.[109] Another approach is to use thresholds to set allocation rules (i.e., to aim at certain targets similar to the targets illustrated in the prevention example earlier, rather than merely making a list). The use of thresholds can enhance transparent and consistent

decision-making.[178] The threshold approach also may be more practical than league tables and mathematical programming techniques because it requires less data and the cost of collecting the additional data may not be worth the expense.[179]

Uses of Cost-Effectiveness Analysis

In its ideal, CEA can help form global health care policy decisions to determine and prioritize the most cost-effective interventions, to deliver these interventions, and to obtain the best possible health in the population for the health care dollar (i.e., the most QALYs for the money). It has received this sort of use in Australia,[180] Canada,[181] and Europe.[182] However, methodological issues[183,184] including those related to standardization[185] and the quality of systematic reviews,[186] the fact that data are not available for all health care interventions, the dearth of appropriate information systems, the difficulty of conveying the degrees and implications of uncertainty in findings,[187] and the lack of clear agreement on policy goals[170,188] have limited the impact of CEA in health care policy decisions. In addition, even a highly cost-effective intervention may be expensive and not affordable. There is an important question of when we make decisions on the basis of cost and when to use cost effectiveness. What is the role of cost in public decision-making?[189] Can we afford expensive but cost-effective treatments or diagnostic tests?

Value judgments also create problems in the use of CEA in policy decisions. For example, is a small benefit for a large number better than a large benefit for a small number? How much should one do for those with short LE? How do we value life versus quality of life? What populations will benefit from a given therapeutic intervention? In addition, technologies and drugs become obsolete, are upgraded and updated, and change in price due to efficiencies, loss of patent protection, and competition. Technologies also have large start-up and development costs, which decline over time. If we perform CEA early and include all these costs, there may be an unrealistic assessment and premature abandonment of a useful intervention.

Overall, a wide range of views exist on the use of CEA, and on the critical obstacles to its wider use. Political factors, technical factors, lack of trust between potential sponsors and users of analyses, lack of training among study consumers, and legal factors are among the reasons more moderate use of CEA in the United States has prevailed.[190] In general, CEA has been used to organize thinking and to aid decision-making (e.g., by the Department of Veterans Affairs in formulary management, by the U.S. Food and Drug Administration and in practice guidelines)[191] rather than as the prime mover in policy. CEA can be used to improve efficiencies, to elucidate and inform specific aspects of an intervention or specific targeted patients, to set prices of drugs or technologies, to create and evaluate incentives, and to constantly test our intuitive assumptions, which may be incorrect (e.g., prevention is not always cost effective and high-technology procedures often are cost effective).

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Chapter 2

The Use of Cardiovascular Drugs: Pharmacological Principles

Stanley Nattel

CHAPTER CONTENTS

This chapter discusses the basic principles that govern the response to cardioactive drugs (see Appendix 1 for a comprehensive list of drugs used in cardiovascular medicine). The general factors that determine the response to a drug are indicated in Figure 2–1A. The factors that determine the relation between drug dose and drug concentration in the plasma are termed *pharmacokinetic factors*. The factors that determine the relation between plasma concentration and drug action are termed *pharmacodynamic factors*.

PHARMACOKINETIC FACTORS

Figure 2–2 summarizes the processes that occur following the administration of any drug. The administration of a drug produces concentrations in a central compartment of blood and highly perfused organs. The drug can be administered by a variety of routes. Most commonly, drugs are administered orally or by subcutaneous, intramuscular, or intravenous injection. The latter are generally referred to as parenteral routes, because they avoid the gastrointestinal (GI) barrier and result in complete or near-complete delivery to the circulation. Occasionally, other routes may be used, such as the buccal, anal (suppositories), or sublingual route. Administration by these alternative routes also bypasses gastrointestinal barriers.

ORAL BIOAVAILABILITY (F)

The GI system absorption of drugs may limit the availability of active compound after oral administration, either because of poor penetration across the mucosal GI barrier (particularly for hydrophilic compounds not subject to active GI transport) or because of rapid first-pass metabolism across the liver. Ouabain, for example, is a digitalis glycoside that is so fat insoluble that it fails to cross mucosal membranes and is useless by oral administration. All compounds crossing the GI mucosa pass through the liver via the portal veins before reaching the systemic circulation. Therefore, rapidly metabolized drugs may be converted so quickly into inactive metabolites (first-pass effect) that they fail to achieve clinically significant quantities in the blood. Lidocaine, for example, crosses the GI mucosa well but is so rapidly metabolized that it is useless as an oral antiarrhythmic.

Bioavailability refers to the fraction or percentage of active compound that reaches the systemic circulation and can achieve the desired clinical effects (often expressed as the fraction, F, of an administered dose that reaches the systemic circulation). Drugs with bioavailabilities lower than 10% generally reach the systemic circulation in insufficient quantities to be effective on oral administration. Drugs with high bioavailability (>80%) are very well absorbed and are not subject to variable responses related to oral absorption. Drugs with limited but acceptable bioavailability may be associated with drug interactions related to their incomplete availability. For example, digoxin has limited bioavailability and can be adsorbed by compounds such as cholestyramine, causing decreased GI availability and a reduced therapeutic response. It is important to distinguish between gastric absorption and functional bioavailability. For example, lidocaine is very well adsorbed after oral administration. However, before it can reach the systemic circulation it has to pass through the liver, where it is rapidly metabolized to byproducts that lack antiarrhythmic efficacy but possess toxic potential. Therefore, lidocaine is not useful as an oral agent. The term *bioavailability* should really be restricted to bioavailability of the compound administered or of that compound and its active metabolites.

In some cases, limited oral bioavailability is used to therapeutic advantage to limit the distribution of a drug to the GI tract. One example is cholestyramine, which acts by binding cholesterol in the gut, promoting its elimination and decreasing serum cholesterol. Its lack of oral absorption makes cholestyramine free of adverse systemic effects. Another example is sodium polystyrene sulfonate (Kayexalate), which binds potassium in the gut and promotes its elimination without any systemic absorption.

VOLUME OF DISTRIBUTION

Following delivery to the blood, drugs are distributed to other tissues. After intravenous administration, many drugs are

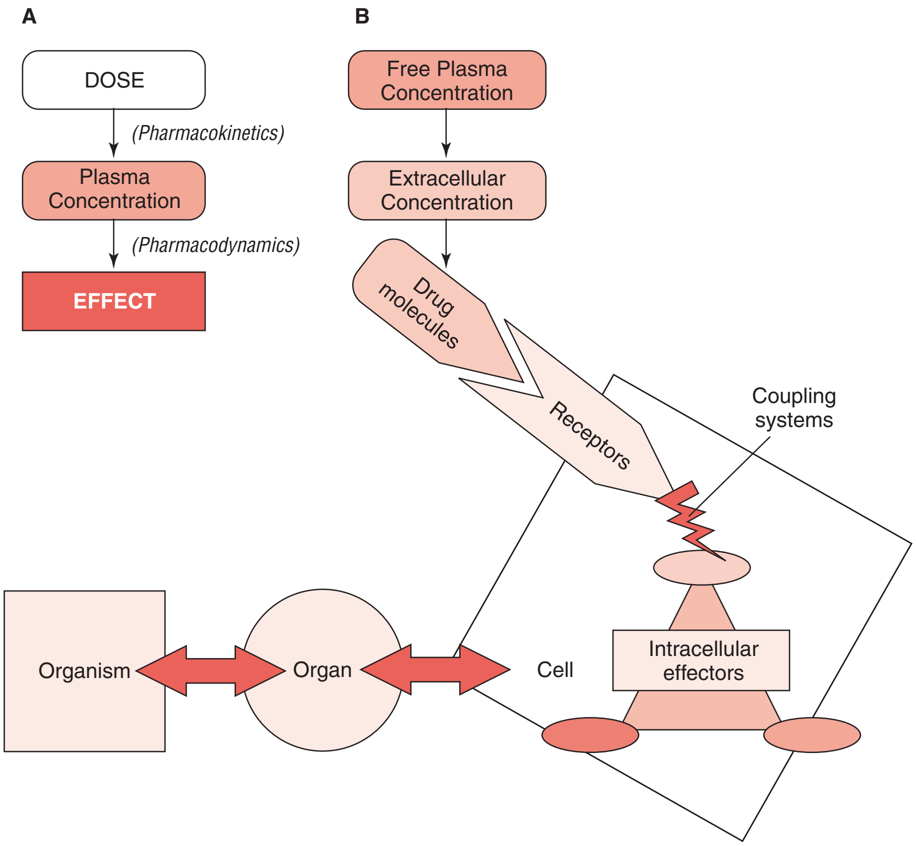

Figure 2–1 **A,** Relation between drug dose and effect. The plasma concentration-dose relation is determined by pharmacokinetic factors, whereas the plasma concentration-effect relation is determined by pharmacodynamic factors. **B,** A schematic showing the processes that mediate the effects of a drug and that determine the relation between plasma concentration and drug effect.

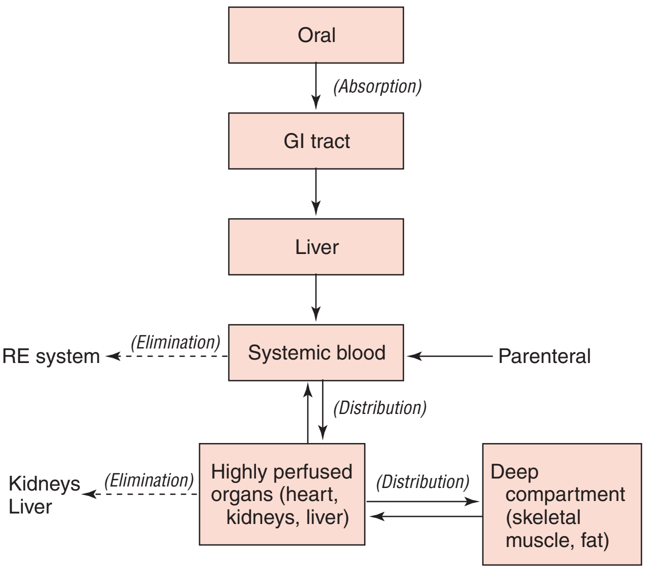

Figure 2–2 Processes that determine the disposition of a drug following administration. GI, gastrointestinal; RE, reticuloendothelial.

distributed rapidly to highly perfused organs (such as the heart and liver), but distribution to less well perfused organs (e.g., skeletal muscle) may take longer. The blood and highly perfused organs are referred to as the central compartment. Immediately after distribution to the central compartment, concentrations may be relatively high, and they decrease rapidly by tissue redistribution, generally with a half-life ($t_{1/2}$) in the range of 5 to 10 minutes. This very rapid decrease in drug concentrations should not be confused with the subsequently slower decrease caused by biotransformation in the liver to inactive metabolites or elimination by renal excretion. Some drugs (e.g., amiodarone) are associated with an even slower second phase of distribution to adipose tissues.

The volume of distribution (V_d) indicates the volume into which the body load of drug would need to be distributed to give the plasma concentration measured after complete distribution. Drugs with a V_d of less than 0.2 L/kg body weight (i.e., less than 14 L for the average adult male) are largely confined to the intravascular space. Drugs with a V_d of greater than 10 L/kg body weight have an extensive peripheral distribution, most commonly in adipose tissue. One striking example is amiodarone, with a V_d of 66 L/kg. The affinity of amiodarone for lipids is so great that prolonged loading is necessary to saturate the body's lipid tissue storage capacity at therapeutic plasma concentrations. This explains, at least in part, the drug's very slow onset of action after the onset of daily dosing, requiring the use of complex loading dose regimens to more rapidly achieve therapeutic effects. The extensive tissue distribution of amiodarone also contributes to its very slow elimination from the body (see later).

PROTEIN BINDING

Many drugs are bound in the blood to plasma proteins, including albumin and α1-acid glycoprotein. In general, protein-bound drug is not available to diffuse into the extra-

cellular space to bathe target tissues and is, therefore, inactive. When relating pharmacological studies of drug actions in in vitro systems to therapeutic drug concentrations, it is important to remember that only drug that is not bound to plasma proteins is physiologically active. Therefore, in vitro concentrations should be related to free plasma drug concentrations ([100% minus protein-bound percentage] times total therapeutic concentration) rather than the total plasma drug concentration during therapeutic administration. Drugs with high protein binding can be displaced by drugs that bind to the same protein and have high therapeutic plasma concentrations, such as sulfa compounds. The latter achieve high enough concentrations to produce near saturation of the considerable plasma protein binding capacity, thereby potentially displacing other drugs highly bound to the same proteins, increasing their free concentration and increasing their activity. An important example is warfarin, which is highly protein bound and can be displaced by drugs such as sulfonamide antibiotics, potentially increasing anticoagulation and the risk of major bleeding.

ELIMINATION AND $T_{1/2}$

Most drugs are eliminated via the liver, the kidneys, or a combination thereof. Disease of the drug-eliminating organ decreases the rate of drug elimination for a given body load and plasma concentration. The maintenance dose must be decreased accordingly or the drug load (and plasma concentration) may increase to the point that potentially toxic effects may be produced. For some drugs, such as warfarin, the hepatic enzyme metabolizing system is indicated because specific enzymes may be inhibited or have their activity induced by specific interacting drugs. This type of interaction is of particular importance for drugs such as warfarin, which have a low therapeutic index and great risk of adverse interactions involving enzyme inhibition (which can precipitate a potentially dangerous bleeding diathesis in patients taking warfarin) or induction (which can reduce warfarin effects to dangerously low levels in patients with a strong indication such as prosthetic cardiac valves).

The $t_{1/2}$ is the drug half-life or time for plasma drug concentrations to decrease by 50%. The $t_{1/2}$ can refer to the rate of tissue redistribution after intravenous administration (the so-called α- $t_{1/2}$) or the rate of elimination following full distribution through the body (the elimination or β- $t_{1/2}$). Elimination half-lives indicate the time for one half of the body load of a drug (or the corresponding plasma concentration) to decrease by 50%. Drugs with a narrow therapeutic index are often given at intervals less than the $t_{1/2}$ to avoid swings in plasma drug concentration greater than 50% (twofold changes).

The $t_{1/2}$ is useful to estimate the time course of changes in plasma concentration. It indicates the time required for plasma concentrations to decrease by 50% after drug discontinuation. Thus, if toxic effects appear, it will take one half-life for 50% of the drug to be eliminated and three half-lives for 87.5% of the drug to disappear from the body. This information is useful for estimating the time at which adverse effects may be expected to disappear after drug discontinuation. Steady-state drug concentrations require four to five half-lives after the onset of dosing or after any dose change. This knowledge may help to avoid misinterpreting responses before steady state has been achieved and may, therefore, help to avoid erroneous dose adjustments. If the organ of drug elimination is diseased, the half-life increases. Correspondingly longer intervals elapse before drug elimination and before steady-state conditions are achieved after beginning the drug or making a dose adjustment. These changes need to be considered in evaluating the time needed for adverse drug effects to cease after drug discontinuation and in estimating drug actions at presumed steady-state effects.

A final point is that, in exceptional cases, the elimination half-life is determined not by the organ of elimination but by extensive tissue stores. Amiodarone is a striking example. Amiodarone achieves extremely high tissue concentrations and is highly protein bound in the blood. Thus, even though the liver is quite efficient at handling the compound, little of the body load exists as unbound drug in the blood available for metabolic biotransformation. This explains the extremely long half-life of the drug, approximately 30 days, after the discontinuation of long-term oral administration.

PHARMACODYNAMIC FACTORS

Pharmacodynamic factors refer to factors that determine the relation between plasma drug concentration and drug effect. Figure 2–1B illustrates the general determinants of drug action at the cellular level. The drug in plasma equilibrates with drug in the extracellular space, producing an effective concentration equal to the free plasma drug concentration. Drug molecules then interact with receptors, which may be intra- or extracellular, and produce changes in intracellular effectors via a coupling system. Altered cellular function will affect the function of the organ, which in turn will alter the state of health of the organism. In some cases (e.g., certain ion channel blockers), coupling to intracellular receptors may not be necessary. Changes in any of the parts of this system (e.g. the number and affinity of the receptors, the activity of the coupling systems, the nature of intracellular effectors) can alter drug sensitivity on a pharmacodynamic basis.

Consider, for example, digitalis action. Digitalis acts by binding to and inhibiting the Na^+, K^+-ATPase in the membrane. The Na^+, K^+-ATPase pumps Na^+ out of the cell in exchange for K^+ which is moved into the cell, to maintain the physiological transmembrane ionic gradient. The positive hemodynamic actions of digitalis result from a tendency for intracellular Na^+ to rise when the Na^+, K^+-ATPase is inhibited. This Na^+ is handled by exchange for extracellular Ca^{2+} (via the Na^+, Ca^{2+}-exchanger, NCX), leading to increased total cellular Ca^{2+} that is handled by increased uptake into the sarcoplasmic reticulum (SR). Digitalis toxicity results when SR Ca^{2+} is so overloaded that spontaneous diastolic spillover from SR Ca^{2+} stores occurs, leading to Ca^{2+}-dependent arrhythmias. A variety of factors can alter the effect of digitalis to promote toxicity. For example, K^+ binds to Na^+, K^+-ATPase and reduces digitalis binding by an allosteric mechanism. If serum $[K^+]$ is reduced, there is less K^+ bound to the ATPase and digitalis action is enhanced, potentially leading to toxicity. If extracellular $[Ca^{2+}]$ is increased (increasing Ca^{2+} entry into cells), or if Ca^{2+} movement into the cell is enhanced (e.g., by catecholamines, theophyllines or acute myocardial ischemia), SR Ca^{2+} stores are increased, increasing the chances of digitalis-

induced excess cell Ca^{2+} loading and toxicity. If NCX activity is increased (e.g., in congestive heart failure) or Na^+, K^+-ATPase activity is reduced, the likelihood of digitalis toxicity is increased.

The pharmacokinetic $t_{1/2}$ should not be confused with the biologic $t_{1/2}$, which may be similar or quite different based on pharmacodynamic considerations. For antiarrhythmic drugs, with a tight concentration-response relation, the pharmacokinetic and biologic $t_{1/2}$ values are similar. On the other hand, for other compounds such as β-adrenoceptor antagonists, they may be quite different. A β-blocker achieves effects by blocking β-adrenergic receptors. The β-adrenoceptor binding is saturable, and low therapeutic concentrations of β-blockers achieve nearly complete saturation. A large increase in β-blocker dose does not produce greater effects because the receptors are already saturated; however, it greatly lengthens the time required after a dose for drug elimination to achieve subtherapeutic concentrations at which β-receptor binding (and blocking) decreases substantially. This principle explains, at least in part, why many drugs can be given at intervals much longer than their pharmacokinetic half-lives.

DOSE

In general, when a sustained effect is needed, maintenance doses need to replace the amount of drug eliminated from the body during the dosing interval. If one knows the desired body load at steady state (for a drug given by intravenous loading dose, this will simply equal that dose) and the percentage of drug eliminated over a dosing interval, one need only multiply the percentage eliminated by the body load to estimate the amount of drug that needs to be given (assuming 100% bioavailability) to maintain the body load constant. The simplest case is when the drug is given at an interval equal to the elimination half-life—then one need give one half the load every half-life to maintain a stable body load and plasma concentrations.

Maintenance doses need to be decreased when the drug-eliminating organ is diseased. In addition, the rate of drug removal from the body is related to the body load. For a given plasma concentration, the body load is generally related to body mass (usually lean body mass). Thus, maintenance doses need to be greater for larger individuals and decreased doses are required for very small patients. Elderly people often have smaller lean body masses and decreased renal function, so they usually require smaller maintenance doses, especially for drugs eliminated by the kidneys. Whenever possible, doses should be titrated to meaningful concentration-related biological effects such as therapeutic endpoints (e.g., International Normalized Ratio or INR for warfarin) or limiting dose-related adverse effects (e.g., hypotension for converting enzyme inhibitors in heart failure).

DRUG INTERACTIONS

Drug interactions can be pharmacokinetic (based on a change in free drug concentration) or pharmacodynamic (based on changes in target organ sensitivity to a given drug concentration). Pharmacokinetic interactions alter the way in which a drug is absorbed, distributed, or eliminated. Reduced GI absorption of a drug on coadministration with cholestyramine is an example of a pharmacokinetic drug interaction related to changed absorption. Reduced drug elimination because of inhibition of hepatic enzymes decreases dose requirements and prolongs drug half-life for a susceptible drug, whereas induction of a drug-eliminating enzyme has the opposite effects (increased dose needs and reduced half-lives). Displacement of a drug from sites of protein binding is an example of an interaction related to changed distribution.

Pharmacodynamic interactions most typically result from drugs with similar or opposite actions. For example, the enhanced bradycardia seen when β-blockers and Ca^{2+} antagonists are coadministered is a pharmacodynamic interaction that may produce adverse effects because of excessive effects of the combined actions of the two classes of drugs. Conversely, reduced efficacy of β_2-agonist bronchodilators in a patient treated with an oral β-blocker is an example of a pharmacodynamic interaction because of opposing drug actions.

PHARMACOGENOMICS

Pharmacogenomics is the study of the genetic factors that determine drug responses. Such factors can operate at either the pharmacokinetic or pharmacodynamic level, and account for a significant degree of the inter-individual variation that can lead to inefficacy or toxicity of an otherwise well-tolerated and effective dose of a drug. This is a rapidly developing field that promises to allow for great improvements in the safety and efficacy of drug therapy by taking into consideration genetic factors that affect dose requirements or the response in individual patients.

It is well recognized that there is substantial inter-individual variation in pharmacokinetic and pharmacodynamic determinants that can greatly affect drug sensitivity and response. The basis for this variation is often unknown, and environmental factors such as drug-metabolizing enzyme inducers and inhibitors are often quite important. However, there may be very clear genetic determinants that are identifiable and would allow for safer and more effective therapeutics. This is an active field of investigation and could be the subject of a voluminous chapter on its own. In the context of the present chapter, I will limit myself to simple illustrative examples.

Oral anticoagulation is strongly indicated for a variety of cardiovascular conditions, such as venous thromboembolism, atrial fibrillation (AF), and prosthetic cardiac valves. The margin of safety for oral anticoagulation is recognized to be narrow, with efficacy requiring international normalized ratios (INRs) of 2 to 3 for AF and 2.5 to 3.5 for mechanical heart valves, and risk of bleeding increasing progressively at INR > 4. Warfarin and other vitamin-K antagonist drugs act by inhibiting the generation of vitamin K from vitamin-K epoxide (Fig. 2–3). The synthesis of vitamin K decreases, leading to impaired vitamin K-dependent γ-carboxylation of glutamyl residues required for activation of a variety of proteins, including several key coagulation factors.

Inter-individual variability in the response to warfarin is great, leading to a risk of inefficacy in some cases and bleeding complications in others. There are important genetic determinants of warfarin sensitivity that act at the pharmacokinetic and pharmacodynamic levels (see Fig. 2–3). CYP2C9 is a

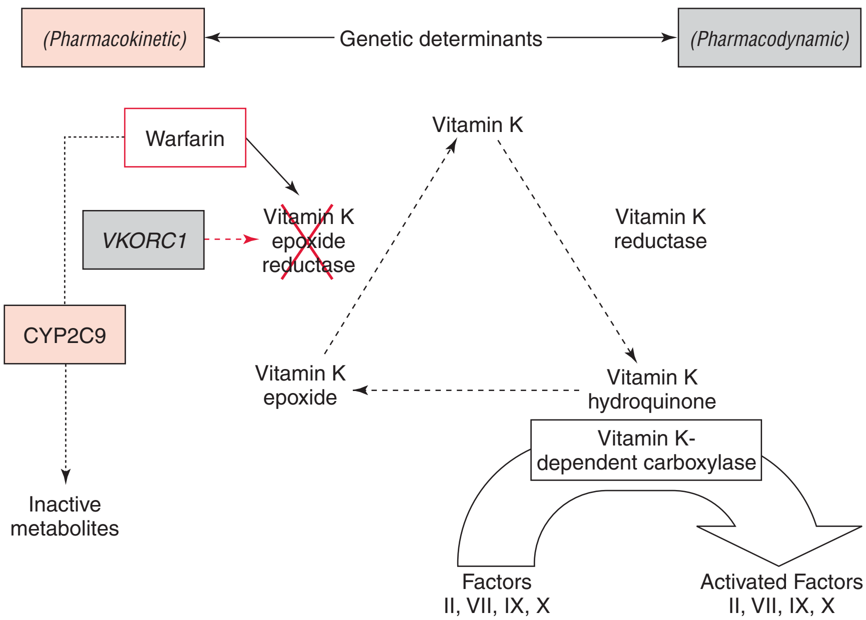

Figure 2–3 Schematic of vitamin K metabolism and its role in coagulation, along with mechanism of action of warfarin and two important pharmacogenomic determinants. Vitamin K is essential for γ-carboxylation of glutamyl residues on coagulation factors required for their activation. Warfarin inhibits vitamin K synthesis from vitamin K epoxide by acting on a crucial reductase enzyme. Key genetic determinants of sensitivity that act on warfarin pharmacokinetics (CYP2C9) and pharmacodynamics *(VKORC1)* are shown. For discussion, see text.

cytochrome P450 enzyme that biotransforms the active *s*-enantiomer of warfarin to inactive metabolites. Single nucleotide polymorphisms (population variants in single nucleotides) greatly affect CYP2C9 activity and can reduce enzyme activity 20-fold—substantially reducing warfarin dose requirements and increasing drug sensitivity/bleeding risk. Mutations in the gene (*VKORC1*) encoding vitamin K epoxide reductase (the enzyme on which warfarin acts) can cause severe warfarin resistance and increase dose requirements by an order of 10-fold. Single nucleotide polymorphisms in *VKORC1* are a significant and identifiable source of variation in vitamin K dose requirements in the population.

It is hoped that the genetic determinants of drug response can be identified for a wide variety of conditions and drugs—with the ultimate goal of obtaining patient-specific pharmacogenomic profiles that allow for safe and effective individualized prescribing.

Suggested Readings

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Gene Therapies and Stem Cell Therapies

CHAPTER CONTENTS

Gene Therapies for Cardiovascular Diseases: Where We Are and Where We Are Going

Luis G. Melo, Christopher A. Ward, and Victor J. Dzau

OVERVIEW

Despite the remarkable therapeutic advances of the last 30 years, cardiovascular disease (CVD) remains the major cause of disability and premature death in the Western World.[1,2] According to epidemiological data published by the National Heart, Lung, and Blood Institute, 20% of the population at age 40 is at risk of developing congestive heart failure (CHF) in their lifetime, and approximately 80% of the population with CHF younger than age 65 will die within 8 years of diagnosis.[2] These staggering statistics have serious socioeconomic repercussions and impose tremendous financial strain on the health care system, calling for new approaches to treat CVD.

The development of tools for genetic manipulation of the cardiovascular system may offer new possibilities for the treatment of cardiovascular diseases.[3-6] Gene transfer can be used as a gain of function strategy to replace or augment the function of defective or undercompensating genes that are involved in disease progression (Fig. 3–1) (for review see reference 6). Strategies for gene silencing have also been successfully used to inhibit genes that are involved in the pathogenesis of CVD (see Fig. 3–1).[6-9] Some of these strategies have progressed to early phase clinical trial testing and others are currently in advanced clinical evaluation (for review see references 6 and 10). Notwithstanding these very significant advances, the successful translation of these novel preclinical therapies into clinical practice will require the development of safe and efficient vectors and delivery tools for gene manipulation.

In this chapter, we use select examples to illustrate the therapeutic potential of these novel strategies in the treatment of common cardiovascular diseases such as coronary artery disease, heart failure, arrhythmias, and vascular diseases.

GENE THERAPIES FOR MYOCARDIAL PROTECTION

The development of gene therapies for acute myocardial infarction (AMI) is not possible with the delivery vectors currently available, because the amount of time required for transgene expression exceeds the time window for successful intervention. For this reason, gene transfer of anticoagulant genes is not feasible as treatment for AMI. The overexpression of cytoprotective genes such as those coding for antioxidant enzymes[11-18] and survival proteins[19,20] has emerged as a potential strategy for myocardial protection from ischemic injury (Table 3–1), and the inhibition of endothelial cell activation may yield some value as anti-inflammatory and immunosuppressive treatment in AMI and in cardiac transplantation[21-23] (for review see reference 24).

Gene Therapy for Protection Against Oxidative Stress-Induced Injury

Because oxidative stress plays a dominant role in myocardial injury, overexpression of antioxidant genes has been proposed as a strategy for protection of the myocardium from reactive oxygen species-induced injury[11-15, 17] (for review see reference 6). The feasibility of antioxidant enzyme gene transfer in long-term myocardial protection from ischemia and reperfusion (I/R) injury was demonstrated using adeno-associated virus (AAV) vector for intramyocardial delivery of heme oxygenase-1 (HO-1), an enzyme that is involved in the catabolism of heme. Overexpression of HO-1 several weeks in advance of

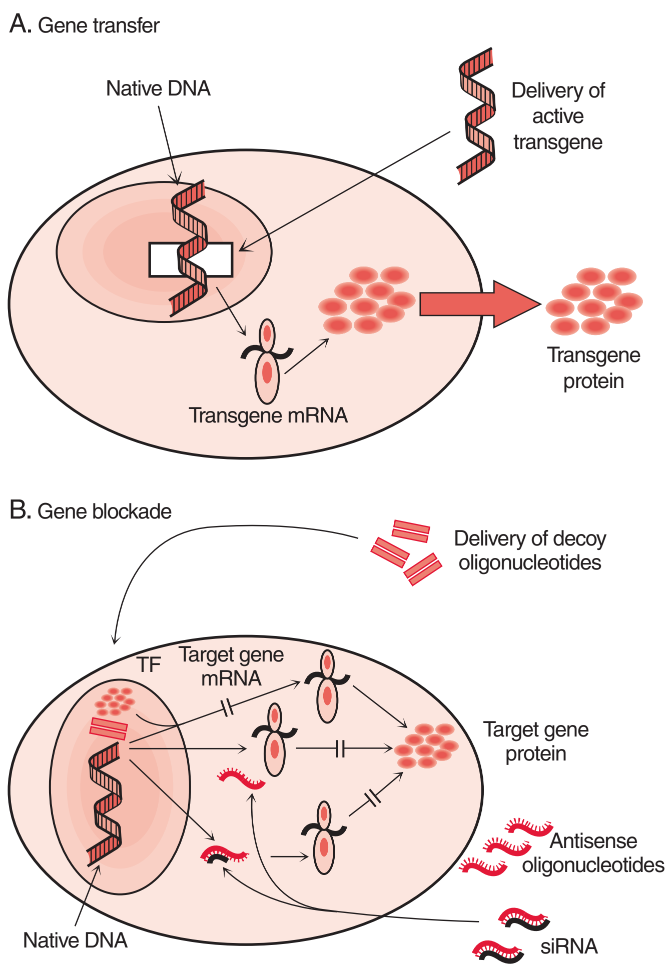


Figure 3–1 Strategies for genetic manipulation in the cardiovascular system. **A,** Gene transfer involves the delivery of exogenous genes (transgenes) by a vector capable of expressing the therapeutic protein in the host cells to increase the activity of the gene(s) (gain of function) whose endogenous function may be deficient and cause disease. **B,** Gene blockade involves inhibition of genes involved in the pathogenesis of disease. Three strategies are commonly used to inhibit gene activity at the transcriptional or translational level. Short single-stranded deoxyoligonucleotides complementary to the target gene mRNA (antisense oligonucleotides) are delivered to the target cells or tissue by transfection or with the aid of a vector. The antisense deoxyoligonucleotide binds to the target mRNA transcript and prevents it from being translated. The second strategy employs double-stranded deoxyoligonucleotides containing the consensus binding sequences (decoy oligonucleotides) for transcriptional factors involved in the activation of pathogenic genes. Transfection of a molar excess of the decoy oligonucleotide prevents the binding and transactivation of the genes regulated by the target transcriptional factor. A novel strategy uses small interfering RNAs (siRNA) to knock down the endogenous activity of pathogenic genes. Less commonly, short segments of RNA with enzymatic activity (ribozymes) are used to degrade target mRNA transcripts.

acute myocardial infarction resulted in approximately 80% reduction in infarct size in rats (Fig. 3–2).[11] The reduction in myocardial injury in the treated animals was accompanied by decreases in oxidative stress, inflammation, and interstitial fibrosis, leading to post-infarction functional recovery, normalization of left ventricular dimensions and increased long-term survival (see Fig. 3–2).[12,13] Significant protection from I/R injury has also been achieved with overexpression of other major antioxidant enzyme systems, such as ecSOD,[14] Cu/Zn SOD,[15] catalase,[15,16] glutathione peroxidase,[17] and stress-induced heat-shock proteins.[18] These findings suggest that preemptive delivery of antioxidant enzymes may be a useful strategy to potentiate endogenous antioxidant reserves for protection of myocardium at risk. Significant myocardial protection from I/R injury has also been reported with overexpression of survival genes such as Bcl-2 and Akt,[19,20] immunosuppressive cytokines[21-24] (for review see reference 25), adenosine A_1 and A_3 receptors[26] and hepatocyte growth factor.[27-29]

Gene Therapy for Myocardial Protection Against Apoptosis and Inflammation

Inhibition of pro-inflammatory genes could be a potential strategy for acute protection from I/R injury. Morishita and colleagues[8] showed that pretreatment with a decoy oligonucleotide capable of inhibiting the transactivating activity of NF-κB reduced myocardial infarct size after coronary artery ligation in rats. The inhibition of adhesion molecule expression could potentially be useful in the treatment of acute myocardial ischemia during cardiac transplantation. For example, treatment with antisense oligonucleotide directed against intercellular adhesion molecule-1 (ICAM-1) was shown to prolong cardiac allograft tolerance and long-term survival if administered ex vivo before transplantation into the host.[22] Others have shown that intracoronary delivery of the immunosuppressive genes TGF-β and interleukin-10 (IL-10) markedly reduced acute rejection and prolonged survival of heterotopically transplanted cardiac allografts,[21] whereas ex vivo intraluminal delivery of NF-κB[23] or E2F[24] decoy oligonucleotide attenuated cardiac allograft arteriopathy both in mice and nonhuman primates. These genetic strategies targeting modulation of the inflammatory and immune responses may have therapeutic potential in the treatment of myocardial infarction and in prevention of acute and chronic transplant rejection (for review see reference 25). In the first case, the inhibition of the inflammatory response in the infarcted myocardium may prevent expansion of the infarct and attenuate chamber remodeling, leading to enhanced long-term post-infarction outcome. In the case of organ transplantation, the transduction of donor organs before transplantation with a vector capable of conferring long-term local expression of immunomodulatory and antiproliferative genes would remove the need for immunosuppressive drug therapy and eliminate the problems associated with its use.

Despite the compelling pre-clinical evidence demonstrating the therapeutic potential of overexpression of cytoprotective genes in myocardial protection, the suitability and efficacy of these therapies for patients with coronary artery disease have not been evaluated. A number of issues remain regarding the feasibility, optimal method of delivery, and time

Table 3–1 Targets for Gene Therapy for Myocardial Ischemic Diseases

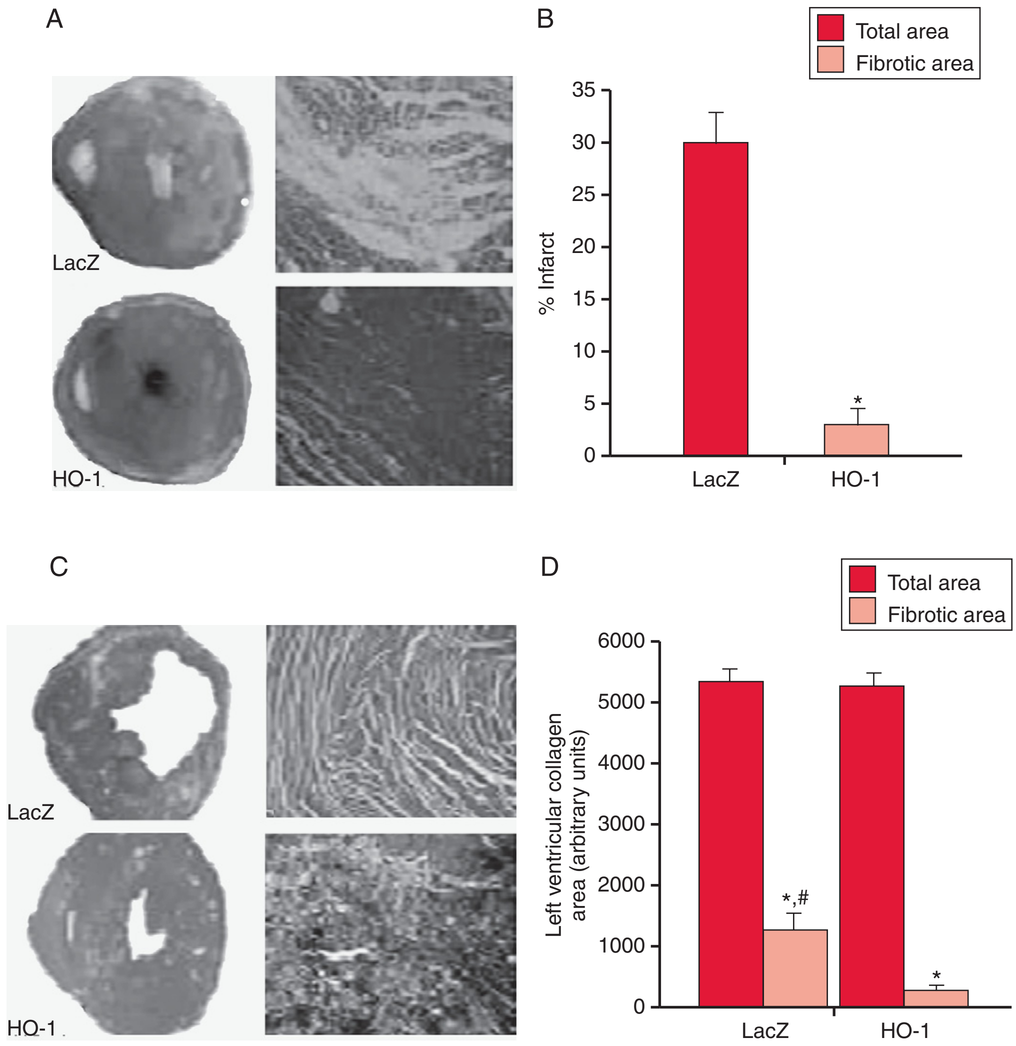
Disease	Therapeutic Target	Genetic Manipulation	Vector	References
Protection/Prevention				
Myocardial infarction	*Antioxidant genes*			
	HO-1, SOD, catalase, GPx	Overexpression	AD, AAV, LV, α-virus	11-17
	Heat shock proteins			
	HSP70, HSP90, HSP27	Overexpression	AD, AAV, LV, α-virus	18
	Survival genes			
	Bcl-2, Akt, HGF	Overexpression	AD, AAV, LV, α-virus	19, 20, 27-29
	Inflammatory cytokines, adhesion molecules and TF			
	I-CAM, V-CAM, TNF-α NF-κB	Inhibition	AS-ODN Decoy ODN AD-AS-ODN	7, 21-24
	Pro-apoptotic genes			
	Bad, caspase inhibitor p 53	Inhibition Fas ligand	AS-ODN Decoy ODN AD-AS-ODN	
	Coronary vessel tone	Overexpression	RV, AD, AAV(?)	26
	eNOS, adenosine (P1, P3) receptors			
Rescue				
Coronary artery disease	*Pro-angiogenic factors*	Overexpression	Plasmid AD, AAV, LV(?)	32-42, 48, 50, 53, 54
	$VEGF_{121,\ 165}$, FGF-1, 2,4, 5, HGF, Ang-1, MCP-1, G-CSF, PDGF-BB, IGF-1,2 HIF-1α/VP16, egr-1, Prox-1			
Heart failure	*Contractility/calcium regulation*	Overexpression	AD, AAV	44, 60-66, 68
	β-adrenergic receptor, SERCA2A BARK, phospholamban	Inhibition	AD, AAV	
Inherited heart disease	*Arrhythmia/channelopathies*	Overexpression/inhibition	AAV	47, 48, 72-74
	SCN5A, I_k, HERG, KCNE1, $G\alpha i_2$, Kir2			
	Cardiomyoplasty	Overexpression	AAV	46
	Sarcomeric proteins, sarcoglycans			
Congenital heart disease	*Heart and blood vessels*	Overexpression	AAV	
	Endoglin, NK×2.5, TBX5, TFAP2B			

AAV, adeno-associated virus; ACS, acute coronary syndromes; ADV, adenovirus, Ang-1, angiopoietin-1; AS-ODN, antisense oligonucleotide; CAD, coronary artery disease; egr-1; early growth response factor-1; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GPx, glutathione peroxidase; HF, heart failure; HGF, hepatocyte growth factor; HIF, hypoxia inducible factor; HO-1, heme oxygenase-1; HSP, heat shock protein; IGF; insulin-like growth factor; I/R, ischemia and reperfusion, LV, lentivirus; MCP-1, monocyte chemotactic protein-1; MI, myocardial infarction; NF, nuclear factor; PDGF, platelet-derived growth factor; RV, retrovirus; SOD, superoxide dismutase; TF, transcription factor; TNF, tumor necrosis factor; V-CAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

of therapeutic gene administration. There are concerns about the potential biodistribution and germ cell line contamination by the vectors, particularly regarding the use of vectors with the capacity for genomic integration such as AAV.[30] These issues are currently being intensively investigated.

GENE THERAPIES FOR MYOCARDIAL RESCUE

Gene therapies for rescuing the ischemic and failing myocardium may be attainable in certain cases. Delivery of



E **Effect of HO-1 gene transfer on post-infarct ventricular hemodynamics by 2-D echocardiography**

PARAMETER	SALINE Pre	SALINE Post	LacZ Pre	LacZ Post	HO-1 Pre	HO-1 Post
IVS (mm)	.157±.0038	.157±.0040	.156±.0049	.171±.0073	.143±.0086	.145±.0106
PW (mm)	.176±.0069	.160±.0062	.176±.0069	.160±.0062	.170±.0088	.162±.0146
LVDD (mm)	.831±.0326	.990±.0069*	.872±.0259	.970±.0082*	.873±.0267	.911±.0350
LVSD (mm)	.550±.0345	.820±.0233*	.541±.0261	.734±.0174*	.577±0.031	.600±.0360
FS (%)	34.1±1.7	17.2±2.0*	38.1±2.4	24.3±1.7*	33.9±2.1	34.2±1.6
EF (%)	71.2±2.2	43.0±3.9*	76.0±2.7	56.5±3.0*	70.9±2.7	71.4±2.0

***P** < 0.05 Pre vs Post

Figure 3–2 (*See also Color Plate 3–2.*) Gene therapy strategy for long-term myocardial protection. The therapeutic gene (HO-1) or reporter gene (LacZ) was delivered by intramyocardial injection to the left ventricle territory supplied by the left anterior descending (LAD) coronary artery; 8 weeks later, ischemia and reperfusion (I/R) injury was induced by ligation and release of the LAD. **A** and **B,** gross (TTC) and microscopic (H&E) histological analysis of the infarcted region 24 hours after reperfusion revealed significant reduction in myocardial injury in the HO-1–treated animals compared with the untreated control animals. **C** and **D,** Marked thinning and remodeling of the anterior left ventricular free wall and interstitial fibrosis were seen 3 months after infarction in the hearts from untreated animals. However, ventricular morphology was preserved in the HO-1–treated animals in association with reduced interstitial fibrosis. **E,** Echocardiographic analysis of left ventricular function and chamber dimensions 1 month after acute myocardial infarction showed normalization of ventricular function (fractional shortening [FS] and ejection fraction [EF]) and left ventricle dimensions (left ventricular diastolic [LVDD] and systolic [LVSD] diameters) in the HO-1–treated animal. (Data modified from Melo LG, Agrawal R, Zhang L, et al: Gene therapy strategy for long-term myocardial protection using adeno-associated virus-mediated delivery of heme oxygenase gene. Circulation 2002;105:602-7 and Liu X, Pachori AS, Ward CA, et al: Heme oxygenase-1 [HO-1] inhibits postmyocardial infarct remodeling and restores left ventricular function. FASEB J 2006;20:207-16.)

pro-angiogenic genes has been reported to promote neovascularization of ischemic myocardium in several animal models and in humans with coronary artery disease[27-29,31-42] (for review see references 6, 11, 31), and genetic manipulation of calcium regulating proteins and β-adrenergic signaling was shown to improve contractile function of failing myocardium (see Table 3–1).[43,44] The use of gene therapy to correct congenital heart and vessel disease is problematic because the genes involved are developmentally regulated.[45] However, gene therapy may have potential in the treatment of some forms of inherited cardiac diseases resulting from single gene mutations, such as arrhythmias and inherited cardiomyopathies.[46-48]

Gene Transfer to Induce Therapeutic Angiogenesis

Evidence of enhanced neovascularization and functional recovery has been demonstrated in several animal models of myocardial and hind limb ischemia after delivery of pro-angiogenic growth factors (see Table 3–1).[27-29,32-35] In all cases, tissue perfusion was improved in association with histological and angiographic evidence of new vessel formation. For example, Mack and coworkers[32] showed improvements in regional myocardial perfusion and left ventricular function in response to stress after delivery of $VEGF_{121}$ in a pig model of chronic myocardial ischemia. Using a similar model, Giordano and associates[33] showed improvement in blood flow and a reduction in stress-induced functional abnormalities after intracoronary injection of human FGF-5 as early as 2 weeks after induction of ischemia, in association with an increase in capillary to fiber ratios. Similarly, intramyocardial delivery of hepatocyte growth factor (HGF) markedly improved post-infarction myocardial blood flow and left ventricular function in dogs,[29] mice,[29] rats,[28,49] and in cardiomyopathic Syrian hamsters[50] in association with enhanced neovascularization.

Despite these findings, there are several outstanding issues relating to the safety and sustainability of therapeutic angiogenesis. It is of paramount importance to put safety measures in place to avert hazardous late-onset side effects such as neovascularizaton of occult neoplasms, retinopathy, or peripheral vascular effects that may result in edema formation or hypotension. For example, Lee and colleagues[51] reported that constitutive overexpression of VEGF led to intramural angiomas followed by heart failure and death, whereas Celleti and coworkers reported that VEGF expression accelerates plaque progression.[52] A possible solution to these problems is to devise tissue-specific vectors incorporating physiologically responsive promoter elements capable of adjusting transgene expression in response to changes in tissue milieu, such as reduced oxygen and inflammation.[53,54] Another approach to achieve regulated therapeutic angiogenesis employs modified transcription factors capable of activating endogenous angiogenic gene expression in response to tissue hypoxia.[55] A novel strategy reported by Amano and colleagues[56] uses a viral vector encoding alterations in the splicing sequences of the VEGF gene to alter the normal ratio of expressed VEGF isoforms. Using this approach, these authors showed that administration of an adenovirus encoding a modification of the splicing sequences for exon 6A to favor expression of $VEGF_{189}$ at the expense of $VEGF_{121}$ led to less pulmonary edema and decreased mortality after intratracheal administration[56] than a vector encoding the three VEGF isoforms in the normal physiological ratios. Regarding the therapeutic sustainability, it will be necessary to establish whether the desired long-term therapeutic effect can be achieved with a single administration of the therapeutic gene or whether multiple treatments may be required. This is an important consideration because angiogenic factor-induced neovessels may regress after termination of transgene expression in the absence of adequate blood supply.[57,58] It is likely that the optimal strategy for therapeutic angiogenesis may require the simultaneous overexpression of multiple genes essential for growth and maturation of new vessels. Several studies are currently under way to evaluate the therapeutic benefit of multi-gene transfer in inducing neovascularization.

Gene Therapy for Rescue of Contractile Function

Rescue of contractile function in the failing myocardium is another potential target for gene therapy. The failing myocardium is characterized by alterations in calcium handling, decreased myofilament sensitivity, excessive catecholamine release, and adrenergic receptor downregulation and desensitization[59]—leading to decreased contractility. The β-AR signaling and calcium-regulating pathways have for several years been used as targets for the treatment of heart failure.[59] Contemporary studies suggest that genetic manipulation of these targets may be useful in the treatment of heart failure. Adenovirus-mediated intracoronary delivery of the β_2-AR gene led to improvements in basal and isoproterenol-stimulated LV contractility and hemodynamic function in rabbits,[60] and rescued β-AR signaling in ventricular myocytes from failing hearts.[44,61] Lai and associates demonstrated that intracoronary delivery of adenovirus expressing adenylate cyclase type VI (AC_{VI}) improved left ventricular function and reduced chamber dilatation in pigs with heart failure,[62] at least in part by restoring β-AR-stimulated cAMP generation.[63]

Gene therapy strategies for normalization of myocardial cytosolic calcium transients have also shown promising results in experimental models of heart failure (see Table 3–1) (for review see reference 43). Intracoronary SERCA2a gene delivery by adenovirus restored systolic and diastolic function concomitant with an increase in basal Ca^{2+}-ATPase activity in a rat model of heart failure induced by aortic coarctation.[64] Furthermore, SERCA2a gene transfer normalized cytosolic transients and restored contractile function in ventricular myocytes isolated from patients with end-stage heart failure.[65] Presumably, overexpression of SERCA2a restores the normal stoichiometry between phospholamban and the Ca^{2+}-ATPase, thereby preventing cytosolic calcium overload and left ventricular dysfunction. Subsequently Cittadini and colleagues[66] showed that intracoronary delivery of the serine threonine kinase Akt1 gene using adenovirus enhanced contractility in normal rats in association with increased systolic Ca^{2+} levels. However, the therapeutic usefulness of Akt as an inotropic agent for the failing heart remains unsettled because this kinase induces cardiac hypertrophy,[67] thus increasing oxygen consumption and energetic cost to perform cardiac work.

The long-term efficacy and safety of adenoviral-mediated myocardial expression of adrenergic and calcium-regulating proteins remain to be established. Sustained expression of the therapeutic transgene may be essential for rescue of the failing

heart. The physiological consequences of chronic β-AR and SERCA2a overexpression are not known. Concerns have been raised that the increase in SERCA2a expression by gene transfer in the failing heart may impose extra demands on myocardial energy expenditure owing to an increased inotropic state, and may cause adverse electrophysiological events such as arrhythmias (for review see reference 68). Such potential adverse effects could accelerate myocardial cell death and precipitate the progression of heart failure. Similarly, increased Akt activity was reported in patients with advanced heart failure,[69] and chronic Akt activation was found to markedly reduce functional recovery after myocardial infarction.[70]

Gene Therapy for Cardiac Arrhythmias

Arrhythmias can be both a cause and consequence of heart failure (for review see reference 71). Current approaches for management of arrhythmias using antiarrhythmic drugs, implantable devices, or radiofrequency ablation are limited by poor efficacy, high cost, and potential risks, indicating the need for alternative approaches for treatment of these diseases. Myocardial delivery of genes encoding defective channel proteins may provide a strategy for correction of the genetic defects associated with inherited and acquired LQT syndromes (see Table 3–1), and the ability to change myocyte electrical behavior by gene transfer has already been documented by several groups.[47,48,72-74] For example, overexpression of potassium channels could be used to reverse the occurrence of ventricular tachyarrhythmias in heart failure. In this regard, Nuss and associates[48] showed that adenoviral transfer of the human K^+ channel gene HERG to adult rabbit ventricular myocytes maintained in primary culture led to abbreviated action potentials and drastically reduced the incidence of early afterdepolarizations after a train of action potentials. This was associated with increased duration of the refractory period. The HERG gene encodes the K^+ channels mediating the faster component of the delayed rectifier potassium current (I_{Kr}) that is critical for myocardial repolarization. The pathophysiological role of K^+ channels mutations in LQT arrhythmias was further established by adenoviral transfer of mutants of the HERG and KCNE1 (I_{Ks}) into the myocardium of guinea pig.[73] Both mutant genes increased beat-to-beat variability and the incidence of early afterdepolarizations. Mutations in both genes have been found in patients with LQT.[71] These findings suggest that K^+ channels responsible for I_{Kr} and I_{Ks} may have potential as targets for gene therapy for prevention of arrhythmias caused by unstable repolarization and heritable LQT disease. Others have demonstrated a therapeutic benefit in the treatment of arrhythmia using gene transfer of G-proteins. For example, Donahue and associates[47] and Bauer and colleagues[72] were able to reduce heart rate following atrial fibrillation in pigs by local delivery of $G\alpha_{i2}$ gene to the atrioventricular node by adenovirus, suggesting that this approach may have application in the treatment of atrial arrhythmia. An alternative approach for heart failure may involve simultaneous transfer of contractility enhancing genes such as SERCA and genes involved in regulation of myocyte electrical activity, such as K^+ channels. Support for this approach was provided by Ennis and colleagues, who showed that co-expression of SERCA1 and the potassium channel Kir2.1 reduces the repolarization time without affecting contractility in guinea pig hearts,[74] suggesting that this strategy may exert synergistic effects in correcting the depressed contractility and delayed repolarization that is commonly seen in heart failure in association with potassium channel downregulation.

Gene Therapy for Inherited Heart Disease

In principle, non-lethal myocardial disease resulting from single gene mutations could be corrected by exogenous delivery of the normal gene. However, the unavailability of vectors capable of efficient long-term gene expression has been a major impediment in the design of rescue therapies for inherited heart disease. Preclinical data support the feasibility of gene therapy for some forms of inherited cardiomyopathy (see Table 3–1). Kawada and colleagues[46] showed that intramyocardial delivery of δ-sarcoglycan to 5 week-old TO-2 Syrian hamsters using an AAV vector completely rescued the progression of cardiomyopathy and markedly increased life expectancy of the treated animals. The design of gene therapies for congenital heart and vessel disease is problematic because the genes involved are developmentally regulated.[45] The ability to intervene and reprogram a defective gene within the crucial developmental time window requires the availability of diagnostic tools that would permit detection of such mutations before the onset of disease or critical developmental events, and access to an effective system for in utero gene delivery. Currently, the prohibitive cost of screening technologies for congenital diseases restricts their use in cases with a strong familial history, thereby leaving many undiagnosed cases.

GENE THERAPIES FOR VASCULAR PROTECTION

Several gene therapy strategies have been developed to reduce vascular tone, plasma cholesterol levels, and vessel wall proliferation in animal models of vascular disease (Table 3–2). The overexpression of vasodilator genes[75-78] or the inhibition of vasoconstrictor peptides[79-83] has been shown to reduce blood pressure in hypertensive animals, and the inhibition of cell cycle progression[9,84-88] or the overexpression of antiproliferative[89-93] or antioxidant[94-97] genes have emerged as useful therapeutic targets for prevention of restenosis and graft atherosclerosis (see Table 3–2). In addition, the overexpression of antithrombotic genes[98-101] and the inhibition of pro-inflammatory and cell-adhesion molecules[102] has shown therapeutic potential for the treatment of thrombosis and inflammation of the vessel wall.

Vascular Tone

Long-term reductions in vascular tone and blood pressure have been achieved in hypertensive animals with exogenous overexpression of vasodilatory genes (see Table 3–2).[75-78] For example, intravenous delivery of a plasmid encoding human endothelial NOS led to a sustained hypotensive effect in SHR rats,[75] and systemic delivery of atrial natriuretic factor,[76] adrenomedullin[77] or kallikrein[78] genes with a constitutively active adenoviral vector decreased blood pressure and attenuates renal and myocardial damage in salt-fed Dahl salt-sensitive and DOCA-salt rats. Another gene therapy strategy for hypertension involves the inhibition of pressor pathways

Table 3–2 Targets for Gene Therapy for Vascular Diseases

Strategy	Therapeutic Target	Genetic Manipulation	Vector	References
	Vasodilation			
Vascular tone	Kallikrein, eNOS, ANP, CNP, HO-1, ecSOD	Overexpression	AD, AAV	75-78
	Vasoconstriction ACE, AGT, AT_1	Inhibition	AAV-AS-ODN	79-84
Atherosclerosis	*Plaque stabilization (CAD)*			
	CD40	Overexpression	AD, AAV(?)	98, 101, 102, 107
	Cholesterol homeostasis			
	LDL-R, lipoprotein lipase, hepatic lipase, Apo-E, VLDL-R, SR-B1, Apo-A1	Overexpression	ADV	102, 108, 110
	Thromboprotection			
	PAI-1, plasminogen activator	Inhibition	AS-ODN	86, 89, 90, 93, 96, 98-101
	Tissue factor, MCP-1			
	t-PA, hirudin, urokinase	Overexpression	ADV, AAV, RV	Tissue factor pathway inhibitor
	Thrombomodulin, COX-1, PGI_2 synthase			
	eNOS, INOS, HO-1, SOD			
Vascular cell proliferation	*Cell-cycle proteins*			
	p16, p21, p27, p53, Rb	Overexpression	Plasmid, ADV, HVJ	9, 85-88
	Cdc2, cdk2, c-myb, c-myc,	Inhibition	AS-ODN,	
	PCNA, E2F,	Inhiibition	Decoy-ODN	
	Cytotoxic/suicide genes			
	Thymidine kinase	Overexpression	ADV	104
	Antiproliferative genes			
	eNOS, INOS, ecSOD, HO-1	Overexpression	ADV, AAV	90-95, 97
	TF, cytokines, apoptotic and signaling molecules			
	NF-κB, $BcL\text{-}X_L$	Inhibition	Decoy-ODN, AS-ODN	
	Fas ligand, Gax, GATA-6	Overexpression	ADV	
	β-interferon, VEGF			

AAV, adeno-associated virus; ACE, angiotensin-converting enzyme; ADV, adenovirus; AGT, angiotensinogen; AT1, angiotensin II-type 1 receptor; ANP, atrial natriuretic peptide; AS-ODN, antisense oligodeoxynucleotide; CAD, coronary artery disease; CNP, C-type natriuretic peptide; COX-1, cyclooxygenase-1; eNOS, endothelial nitric oxide synthase; HF, heart failure; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor kappa B; PCNA, proliferating cell nuclear antigen; PGI2 synthase, prostacyclin synthase; PAI-1, plasminogen activator inhibitor-1; RV, retrovirus, SOD, superoxide dismutase; TPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

using antisense oligonucleotides against components of the renin-angiotensin system (RAS)[79-82] or the β-adrenergic signaling pathway.[83] Using AAV for intravenous delivery of angiotensinogen antisense cDNA, Tang and coworkers[79] showed a dose-dependent decrease in arterial blood pressure in spontaneously hypertensive adult rats (SHR) in association with reduced angiotensinogen levels, and Kimura and coworkers[80] reported that the onset of hypertension was delayed up to 6 months in SHR after a single intracardiac injection of angiotensinogen antisense cDNA in newborn SHR rats. Comparable results were reported with antisense inhibition of angiotensin converting enzyme[81] or AT_1 receptor.[82] Sustained reduction in blood pressure has also been achieved by antisense inhibition of β_1-adrenergic receptor,[83] suggesting that this strategy could be used as an alternative to pharmacological β-blockade.

The therapeutic efficacy of antihypertensive gene therapy has not been assessed in humans despite its simplicity, safety, and apparent efficacy. Enthusiasm for these novel approaches is moderated by the clinical efficacy of current antihypertensive drugs. Nevertheless, the prospect of achieving long-term control of blood pressure in hypertensive patients by gene therapy is an attractive feature that could overcome the problem with compliance often manifested by patients on antihypertensive drugs.

Neointima Proliferation

Percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) are the current treatment options for patients with coronary artery disease requiring revascularization. However, the failure rate of these proce-

dures owing to restenosis and atherosclerosis remains relatively high, despite the introduction of novel drug-eluting stents. The ability to inhibit proliferation of the medial smooth muscle using gene therapy techniques provides the opportunity to genetically engineer native vessels and grafts to render them resistant to atherosclerosis and neointimal hyperplasia (for review see references 84, 103).

Two anti-restenosis gene therapy strategies have been used to inhibit neointimal hyperplasia, using a wide variety of therapeutic targets. Cytostatic strategies involve the inhibition of key proteins regulating cell cycle progression to arrest neointimal cell proliferation (see Table 3–2).[85-88] We used this strategy to treat jugular veins in vivo with hemagglutinating virus of Japan (HVJ)-liposome complexes containing antisense oligonucleotide against cell-cycle regulators proliferating cell nuclear antigen (PCNA) and cdc2 kinase in atherosclerotic New Zealand rabbits before carotid artery interpositional grafting.[87] The gene therapy led to adaptive remodeling of the graft, successfully inducing medial hypertrophy while inhibiting neointimal hyperplasia, to yield conduits that resemble normal arteries.[88] Subsequent histological and functional analyses of the treated vein graft showed marked inhibition of graft atherosclerosis, decreased inflammation, and improved endothelial function (Fig. 3–3).[88] Subsequently, it was reported that the treatment of vein grafts before implantation with a decoy deoxyoligonucelotide bearing the consensus binding sequence of E2F-1, a transcriptional factor involved in cell-cycle progression, resulted in prolonged resistance to neointimal hyperplasia and improved patency of the graft after transplantation.[9] An interesting variant in cytostatic gene therapy involves the targeted expression of the thymidine kinase gene. The gene renders the transduced cells sensitive to antiviral drugs such as ganciclovir, such that treatment with the drugs eradicates the vector targeted cells. This strategy, commonly known as *suicide gene therapy,* has been used successfully to reduce neointima proliferation in atheromatous iliac arteries from rabbits.[104]

Delivery of antiproliferative genes such as those coding for the nitric oxide synthases offers another approach to achieve inhibition of neointimal hyperplasia (see Table 3–2). All three isoforms of nitric oxide have been shown to exert vasculoprotective and antiproliferative effects after gene transfer (for review see reference 89). Endothelial and iNOS gene transfer are equally efficacious in reducing neointimal thickening in balloon-injured vessels.[90-93] Local delivery of antioxidant enzymes such as HO-1[94,95] and ecSOD[96,97] by adenovirus has also been shown to inhibit neointima hyperplasia in various animal models of restenosis, possibly owing to reduction in inflammation and oxidative stress during the early phase of vascular injury.

Atherosclerosis and Thrombosis

Plaque rupture and subsequent thrombosis and occlusion are the major causes of acute coronary episodes that result in myocardial infarction and sudden cardiac death.[105,106] Gene therapy aimed at reducing the cholesterol level and/or at increasing thromboresistance and tensile strength within the plaque could potentially offer the possibility to achieve long-term plaque stabilization and prevent the occurrence of acute coronary events (see Table 3–2).[107] For example, the over expression of apoprotein ApoA-1 in mice by intravenous adenoviral gene delivery increases serum HDL levels,[108] whereas the blockade of monocyte infiltration and activation in the arterial

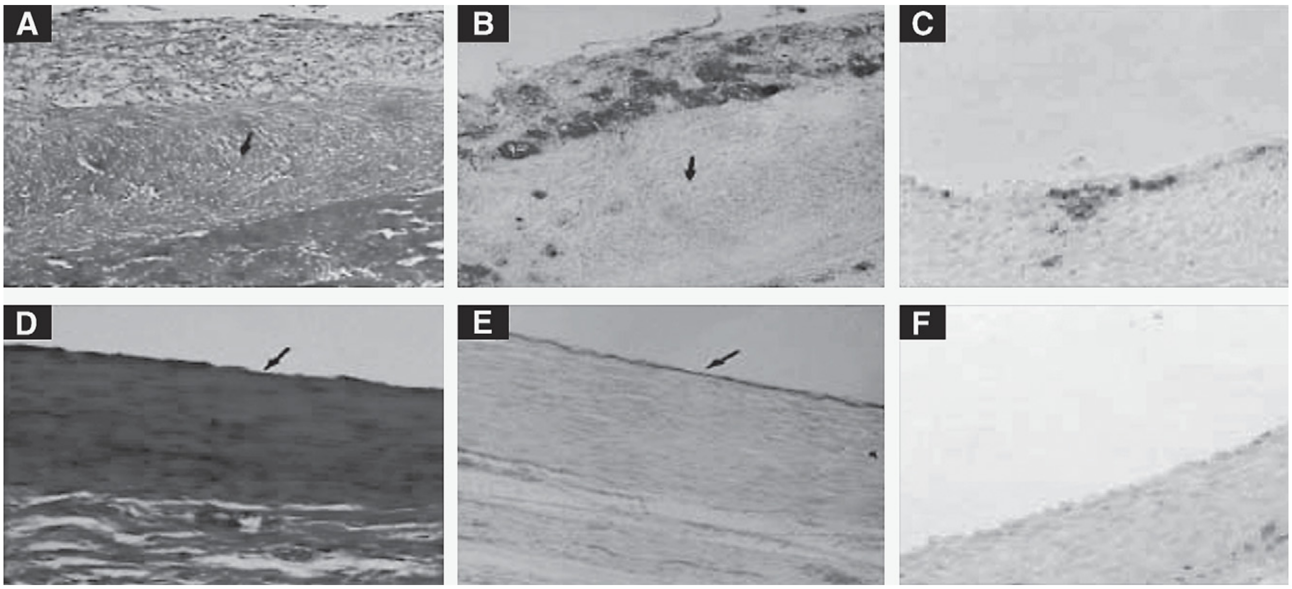


Figure 3–3 (*See also Color Plate 3–3.*) Intraoperative genetic engineering of atherosclerosis-resistant vein grafts by selective inhibition of cell cycle regulatory genes cdc2 kinase and proliferating cell nuclear antigen (PCNA) using antisense deoxyoligonucleotides. **A-C,** Jugular vein grafts from hypercholesterolemic rabbits 6 weeks after carotid inter-positional grafting showed significant neointima hyperplasia (**A**), infiltration of foam cells throughout the intima and subendothelial regions (**B**), and increased adhesion molecule (VCAM-1) expression (**C**). **D-F,** Selective blockade of cdc2 kinase and PCNA in hypercholesterolemic rabbits leads to inhibition of neointimal deposition (**D**), significantly reduced foam cell accumulation and plaque formation (**E**) and inhibition of adhesion molecule (VCAM-1) expression (**F**).

continued

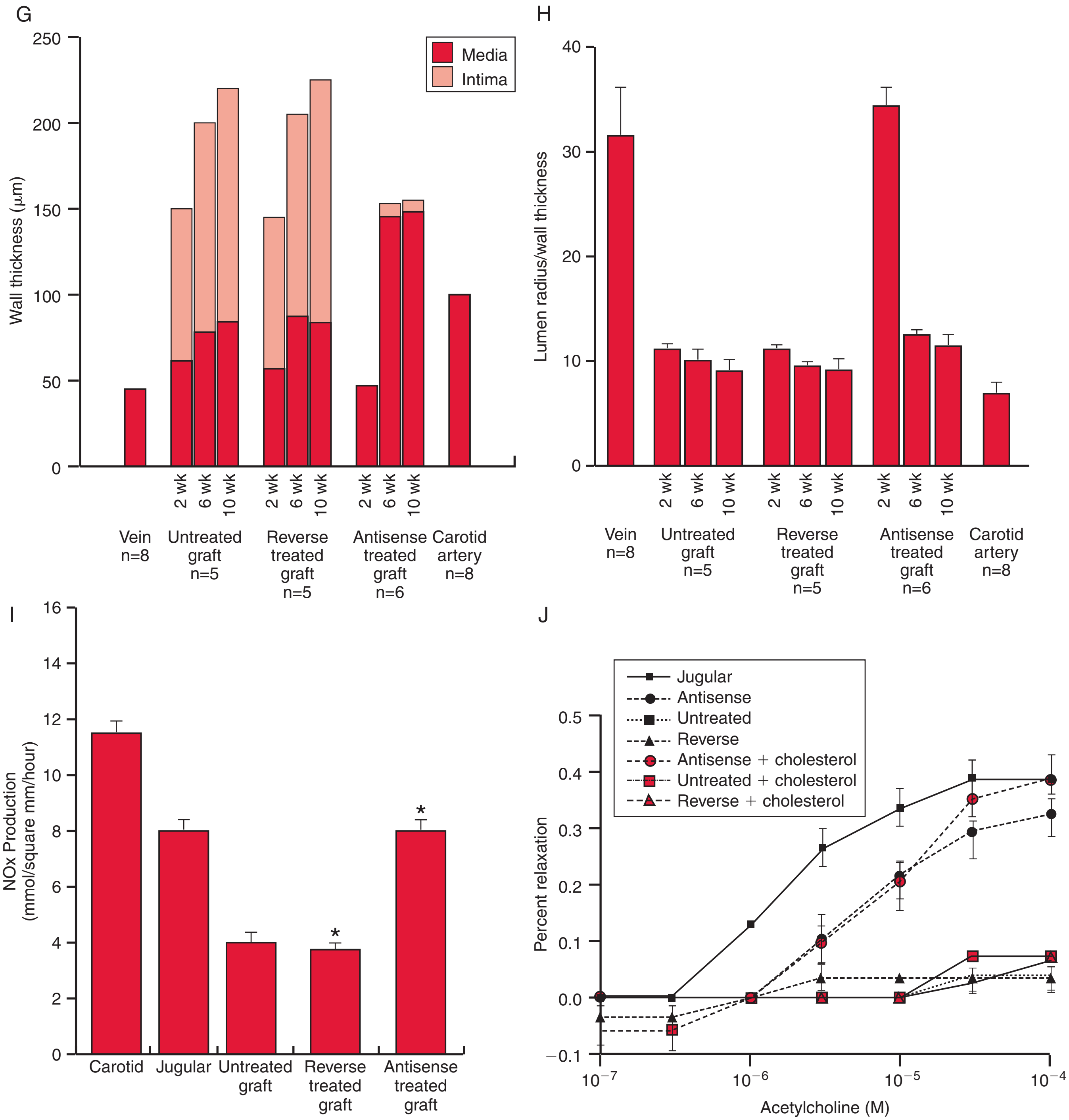


Figure 3–3, cont'd **G-H,** Inhibition of cdc2 and PCNA with the antisense oligonucleotides promoted positive remodeling of the vein graft characterized by increased media hypertrophy and reduced neointima hyperplasia to yield fully arterialized conduits. **I-J,** Treatment of the vein grafts with the antisense deoxyoligonucleotide resulted in increased nitric oxide production (**I**) and improved endothelial function (**J**). (Data modified from Mann MJ, Gibbons GH, Kernoff RS, et al: Genetic engineering of vein grafts resistant to atherosclerosis. Proc Natl Acad Sci U S A 1995;92[10]:4502-6 and Mann MJ, Gibbons GH, Tsao PS, et al: Cell cycle inhibition preserves endothelial function in genetically engineered rabbit vein grafts. J Clin Invest 1997;99[6]:1295-301.)

wall by inhibition of monocyte chemoattractant protein-1 (MCP-1) receptor activation was shown to retard the onset of atheroma and to limit progression and destabilization of established atherosclerotic lesions in ApoE deficient mice.[102] Another important target for vascular protection is eNOS (for review see reference 89). Endothelium-derived NO exerts a plethora of vasculoprotective actions, including vasorelaxation, inhibition of VSMC proliferation and migration, and inhibition of platelet activation and adhesion.[109] NOS gene transfer provides a mechanism to increase NO bioac-

tivity and enhance the antiatherogenic properties of the vessel wall. For example, gene transfer of eNOS reduces inflammatory cell infiltration and lipid deposition in carotid arteries of cholesterol-fed rabbits.[93] Gene transfer of cytoprotective genes such as HO-1 and SOD has also been shown to exert vasculoprotective effects. Adenovirus-mediated delivery of HO-1 attenuated the development of aortic lesions in ApoE-deficient mice, in parallel with a decrease in iron deposition,[95] and delivery of manganese superoxide dismutase gene improved vascular function in pre-atherosclerotic carotid arteries from hypercholesterolemic rabbits.[96]

Lipid-lowering gene therapy may be useful in the treatment of inherited disorders of lipid metabolism such as familial homozygotic hypercholesterolemia (FHH) and apoE deficiency because of their refractoriness to medical treatment. For these patients, gene therapy may offer hope for a cure because of the monogenic nature of these diseases. The use of lipid-lowering gene therapy in patients with FHH has, to date, been evaluated only in a small phase I feasibility clinical trial.[110] Three out of five patients treated with a retroviral vector expressing the wild-type LDL receptor showed a reduction of 6% to 23% in plasma LDL levels, but the duration of gene expression was short, possibly due to endogenous retroviral silencing. The development of clinically effective therapies for FHH and apoE deficiency will be dependent on the availability of vectors capable of providing stable, long-term expression of the therapeutic gene. This will require a vector capable of chromosomal integration without triggering insertional mutagenesis. Furthermore, the need for long-term therapeutic gene expression will require tissue-specific regulated expression of the transgene to avert potential cytotoxic effects of transgene expression. One potential strategy is to use a physiologically-regulated AAV vector for skeletal muscle or liver-specific expression of ApoE or the LDL receptor (for review on regulatable vector systems see reference 111).

CLINICAL GENE THERAPY

Despite the compelling pre-clinical evidence about the feasibility and efficacy of gene therapy in the treatment of cardiovascular diseases, only a few small-scale trials have been carried out.[112] Of the 918 trials that have been finished or currently under way worldwide, only 8.3% are in cardiovascular disease. The majority of these trials evaluated the therapeutic efficacy of angiogenic gene transfer in the treatment of coronary and peripheral ischemia (Table 3–3)[36-38, 41, 113-128](for review see references 112, 129). Although the trials generally support the feasibility and safety of angiogenic gene transfer, the clinical findings have been inconclusive with regard to the efficacy of angiogenesis gene therapy. In a phase I study in five male patients 53 to 71 years of age with CAD who did not respond to conventional anti-angina therapy, intramyocardial delivery of naked plasmid encoding $VEGF_{165}$ into the ischemic

Table 3–3 Clinical Trials Using Gene or Protein Therapy for Therapeutic Angiogenesis in Myocardial and Peripheral Ischemia

Trial Name/Authors	Trial Phase	Therapeutic Agent	Vector and Route of Administration	Therapeutic Target	Follow-up	Therapeutic Outcome
Losordo et al., Circulation 1998;98:2800	I	$VEGF_{165}$	Plasmid, intramyocardial	CAD not amenable to revascularization	10 Wk	↑ SPECT-sestamibi, ↑ Rentrop score, ↓ NTG use
Losordo et al., Circulation 2002;105:2012	I/II	$VEGF_{165}$	Plasmid, transendocardial with NOGA catheter	CAD not amenable to revascularization	12 Wk	↑ CCS angina class, ↑ exercise duration, ↑Seattle angina questionnaire
Vale et al., Circulation 2001;103:2138	I	$VEGF_{165}$	Plasmid, transendocardial with NOGA catheter	CAD not amenable to revascularization	1 Yr	↑ SPECT-sestamibi, ↑ Rentrop score, ↓ NTG use, ↓ weekly angina attacks
Symes et al., Ann Thorac Surg 1999; 68:830	I	$VEGF_{165}$	Plasmid, intramyocardial	CAD not amenable to revascularization with type III-IV angina	3 Mo	↑ SPECT-sestamibi, no rest ischemic pain, ↓ NTG use
Rosengart et al., Circulation 1999; 100:468	I	$VEGF_{121}$	Adenovirus, intramyocardial	CAD not amenable to revascularization	1 Mo	↑ SPECT-sestamibi, ↑ CCS angina class, ↑ treadmill exercise
Hedman et al., Circulation KAT trial 2003; 107:2635	I	$VEGF_{121}$	Adenovirus, intracoronary	CAD at time of PTCA	6 Mo	↓ Coronary restenosis, ↑ myocardial

continued

Table 3–3 Clinical Trials Using Gene or Protein Therapy for Therapeutic Angiogenesis in Myocardial and Peripheral Ischemia—cont'd

Trial Name/Authors	Trial Phase	Therapeutic Agent	Vector and Route of Administration	Therapeutic Target	Follow-up	Therapeutic Outcome
Henry et al., Circulation VIVA trial 2003;107:1359	I	$hrVEGF_{165}$ protein	Intracoronary with intravenous suppl.	CAD not amenable to revascularization	2 Mo	No change in ETT, ↓ angina episodes
Grines et al., AGENT trial Circulation 2002; 105:1291	I/II	FGF-4	Adenovirus, intracoronary	Class II or III angina, >1 vessel patent	1-3 Mo	↑ ETT, improved stress ECG
Simons et al., FIRST trial Circulation 2002;105:788	I/II	FGF-2	Intracoronary bolus	Class II or III angina	90 and 180 day	↑ ETT, ↓ angina episodes at 90 day No differences at 180 day
Laham et al., J Am Coll Cardiol 2000; 36:2132	I	FGF-2	Intracoronary infusion	CAD not amenable to revascularization	1-6 Mo	↑ETT, ↑ wall thickness and perfusion by MRI, improved quality of life
Unger et al., Am J Cardiol 2000; 85:1414	I	FGF-2	Intracoronary bolus	CAD with stable angina	1 Mo	↑ Diameter of epicardial arteries
Kleiman et al., J Am Coll Cardiol 2000; 36:310	I	FGF-2	Intracoronary infusion	CAD not amenable to revascularization	6 Mo	No differences between placebo and treatment groups
Schumacher et al., Circulation 1998;97:645	I	FGF-1	Intramyocardial	Three vessel disease and distal LAD disease	12 Wk-3 yr	↑ Angiogenesis distal to LAD, ↑ SPECT-sestamibi, ↓ NTG use
Seiler et al., Circulation 2001;104:1994	I	GM-CSF	Intracoronary subcutaneous	CAD not amenable to revascularization	2 Wk	↑ Coronary flow index, ↓ ECG abnormalities during balloon inflation
Baumgartner et al., Circulation 1998;97:1114	I	$VEGF_{165}$	Plasmid, intramuscular	Critical limb ischemia	2-11 Mo	↑ Ankle-brachial index, ↑ exercise time, ↑neovascularization, limb salvage
Makinen et al., Mol Ther 2002; 6:127	I	$VEGF_{165}$	Adenovirus, intraluminal after PTA	Critical limb ischemia and infrainguinal occlusion	3 Mo	↑ Neovascularization, ↑ ankle-brachial index
Isner et al., Lancet 1996; 348:370	I	$VEGF_{165}$	Plasmid, intraluminal	Critical limb ischemia	3 Mo	↑ Neovascularization and Doppler flow
Lederman et al., TRAFFIC trial Lancet 2002; 359:2053	I	FGF-2	Intraluminal	Critical limb ischemia with intermittent claudication	3 Mo	↑ ETT

CAD, coronary artery disease; ETT, exercise tolerance time; LAD, left anterior descending coronary artery; NTG, nitroglycerin; PTA, percutaneous transluminal angioplasty

myocardium led to reduction of anginal symptoms and improvement, albeit modest, in left ventricular function concomitant with reduced ischemia.[38] Vale and colleagues[39] reported significant reductions in weekly anginal attacks and reduced nitroglycerin consumption in six patients with chronic myocardial ischemia for as long as 1 year after catheter-based delivery of naked VEGF-2 (VEGF-C) assisted by electromechanical NOGA mapping of the left ventricle. SPECT-sestamibi scanning of these patients showed improved myocardial perfusion for up to 90 days in the patients treated with the gene. These authors have subsequently completed a phase 1/2 placebo-controlled, double-blind, dose-escalating trial using the same NOGA-assisted catheter-based delivery of VEGF-2 in 19 no-option patients (average age, 61 years) with Canadian Cardiovascular Society class III or IV angina.[40] Endpoint analysis at 12 weeks after treatment showed an improvement in anginal symptoms with reduced ischemic area and increased exercise tolerance in the patients treated with the VEGF-2 gene, whereas no improvement was seen in the placebo control patients.[40] Similar results were reported for the EUROINJECT-ONE trial.[113] In this phase II randomized double-blind trial, 80 no-option patients were treated by intramyocardial injection of a plasmid-encoding human VEGF-A_{165} (ph VEGF-A_{165}) ($n = 40$) or placebo plasmid ($n = 40$) using the NOGA mapping system to deliver the plasmid to the area showing stress-induced perfusion defects. Three months after plasmid delivery, no improvement in stress-induced perfusion defects was seen in the VEGF-A_{165}-treated patients compared with the patients receiving the placebo.[113] However, the VEGF-A_{165}-treated patients showed improved regional wall motion as assessed by NOGA and contrast ventriculography.[113,114]

Another randomized, placebo-controlled, double-blind phase II trial, the Kuopio Angiogenesis trial (KAT), evaluated the safety and feasibility of catheter-based intramyocardial delivery of Ad-$hVEGF_{165}$ or $hVEGF_{165}$-liposomes in patients (mean age 58 ± 6 years) with CCS classes II and III angina undergoing percutaneous coronary angioplasty (PCA) and stenting.[115] Follow-up at 6 months did not show any significant differences in the rate of restenosis among the two $hVEGF_{165}$ groups of patients and the placebo controls. However, myocardial perfusion was slightly (6%) but significantly increased in the Ad-$hVEGF_{165}$ treated patients[115] compared with pre-treatment values, suggesting that intracoronary delivery of angiogenic cytokines at the time of PCA may be a useful adjuvant therapeutic strategy to enhance coronary perfusion in patients with coronary artery disease undergoing surgical revascularization. Interestingly, despite the decrease in perfusion defect score, no significant improvement was seen in exercise time and rate pressure product in the Ad-$hVEGF_{165}$-treated patients.

Gene transfer of other angiogenic cytokines, such as fibroblast growth factor (FGF), has also been evaluated for treatment of ischemic heart disease. The Angiogenic GENe Therapy (AGENT), a phase I/II double-blind, randomized, placebo-controlled trial examined the effect of dose-escalating adenovirus-mediated intracoronary delivery of FGF-4 in 79 patients (mean age, 65 years) with CCS class II and III stable angina.[116] The results of this trial showed a general trend toward an increase in exercise tolerance and improved stress echocardiograms at 4 and 12 weeks after gene transfer in the patients treated with FGF-4 gene therapy compared with the patients receiving placebo, in association with angiographic evidence of neovascularization.[116] However, the trial was not sufficiently powered to detect statistically significant differences between the treated and placebo groups in the treadmill exercise time to fatigue, and the outcome beyond 12 weeks has not been reported for these patients. Nevertheless, the trial showed that the therapy was safe and well tolerated. Subsequently, the results of the AGENT 2 study were reported by the same group.[117] The trial assessed the effect of intracoronary AdFGF-4 gene transfer or placebo on myocardial perfusion in 52 patients (mean age, 58 years) with stable angina 8 weeks after gene transfer. Using stress-related reversible perfusion defect size (RPDS) as the primary endpoint, the results of this trial showed a decrease in RPDS and improved perfusion in the AdFGF-4-treated group ($n = 35$) compared with the placebo group ($n = 17$), but the difference did not reach statistical significance, presumably owing to the confounding effect of an outlier in the placebo group. In addition, no significant differences between the two groups were found in angina parameters (Canadian Cardiovascular Society angina class); however, a greater number of patients in the AdFGF-4-treated group reported complete resolution of anginal symptoms and no nitroglycerin use.[117] Subsequently, the AGENT 3 and 4 trials have been carried out. The AGENT 3 trial completed enrollment and follow-up of several hundred patients, but no differences were found between the AdFGF-4 and placebo-treated patients in all the primary and secondary endpoints. The AGENT 4 trial was subsequently cancelled on release of the AGENT 3 results (unpublished, for discussion on AGENT trials, please see lecture by Patrick Serruys at the 69th scientific session of the Japanese Circulation Society).

Some trials have also been undertaken to evaluate the effect of cell cycle inhibition on neointima proliferation and vein graft failure. A phase I prospective, randomized double-blind trial of human saphenous vein graft treatment with E2F decoy (Project In Ex-Vivo Vein Graft Engineering Via Transfection, PREVENT-1) was carried out in high-risk patients suffering from peripheral arterial occlusive disease.[118] Using nondistending pressure to deliver the E2F decoy oligonucleotide ex vivo before arterial interpositional grafting, we demonstrated that E2F decoy treatment was safe and feasible. Although the results were preliminary, the study provided evidence that cytostatic gene therapy is feasible for clinical application. Subsequently, PREVENT II has largely confirmed the finding of the PREVENT I trial. PREVENT II was a randomized double-blind, placebo-controlled phase II trial designed to evaluate the effect of E2F decoy treatment on CABG failure in 202 patients (one half was treated with E2F decoy) undergoing bypass surgery for at least two vessels.[119] The interim results confirmed the feasibility and safety of E2F-1 decoy. Analysis of the secondary endpoints using quantitative coronary angiography and 3-dimensional intravascular ultrasound demonstrated increased patency and adaptive vessel remodeling characterized by reduction in neointimal size and volume in the treated group 1 year after treatment, leading to a 40% reduction in critical stenosis. The results of the PREVENT IV trial have been published.[120] This phase III, multicenter, randomized double-blind, placebo-controlled trial evaluated the therapeutic efficacy of ex vivo treatment of autologous vein grafts with E2F decoy (Edifoligide) in 3014 patients from 107 sites undergoing CABG. The primary endpoint evaluated was vein graft failure, defined as death or

>75% stenosis in treated vein grafts at 12 to 18 month angiographic follow-up. The results showed that Edifoligide was no more effective than placebo in preventing graft failure 12 to 18 months after CABG surgery,[120] and the authors concluded that a longer follow-up period will be necessary to determine whether treatment with the E2F decoy has delayed beneficial effects to improve the durability of CABG surgery.

A number of early phase clinical trials of angiogenic gene therapy have also been carried out in patients suffering from peripheral artery disease.[121-128] Intra-arterial delivery of $phVEGF_{165}$ to a group of 62 patients with critical limb ischemia and 28 patients with intermittent claudication led to indices of enhanced collateral vessel development, including increased ankle-brachial and toe-brachial index, improvement of ischemic gangrene, and disappearance of ischemic rest pain. However, 34% of the treated patients also presented with lower-extremity edema, likely due to the effects of VEGF in increasing vascular permeability.[121] Subsequently, Makinen and colleagues[122] reported the results of a phase II randomized, placebo-controlled, double-blind study in which 35 patients with chronic lower limb ischemia were treated by catheter-based delivery Ad-$hVEGF_{165}$ (n = 18) or $hVEGF_{165}$-liposome (n = 17) at time of percutaneous transluminal angioplasty. Three months after gene delivery, digital subtraction angiography revealed increased vascularity distal to the site of gene delivery in both treated groups compared with the control group (n = 19) receiving Ringer's lactate. However, the ankle brachial index did not differ between the groups.[122] In another phase II dose-finding multicenter trial (RAVE, Regional Angiogenesis with Vascular Growth Factor), the authors treated 105 patients (n = 35-36 patients per group) with severe intermittent claudication by intramuscular injection of Ad-$VEGF_{121}$ at twenty sites in the muscles of the lower leg requiring revascularization, and then evaluated the change in peak walking time at 12 weeks as the primary endpoint.[123-126] The results of the RAVE trial were negative and did not yield significant differences between the Ad-$VEGF_{121}$-treated patients and the control patients in peak walking time, ankle-brachial index, claudication onset time, and quality of life measures,[126] thus failing to provide support that local delivery of a single dose of Ad-$VEGF_{121}$ may be useful in the treatment of patients with unilateral peripheral artery disease. Subsequently, Morishita and associates[127] reported the results of a small safety and feasibility trial using intramuscular injection of hepatocyte growth factor (HGF) plasmid in six patients with critical limb ischemia. No adverse effects were reported in association with the gene therapy and no peripheral edema was observed. The authors reported that the diameter of 8 out of 11 ischemic ulcers in 4 patients was reduced by >25%. These results, although preliminary, suggest that HGF gene transfer may have therapeutic potential in the treatment of peripheral artery disease and warrant larger, controlled trials.

The ability to induce therapeutic neovascularization by gene transfer has, so far, been disappointing. The success of clinical gene therapy will ultimately be determined by the ability to resolve the outstanding issues regarding safety and efficacy. Larger and more adequately controlled multicenter trials are warranted. Stringent criteria need to be applied in the selection of patients. For example, candidates for therapeutic angiogenesis often have an impaired angiogenic response because of underlying endothelial dysfunction.[58] In addition, objective endpoints for assessing efficacy need to be standardized and implemented, as well as measures to assess and overcome potential short- and long-term complications, such as edema, hypotension, retinopathy, and neovascularization of occult neoplasms. The issues surrounding therapeutic patency and sustainability of neovessels have not been adequately addressed. The ideal gene therapy strategy for therapeutic angiogenesis will likely require the simultaneous expression of multiple genes involved in the various steps of vessel development, growth, and maturation. Furthermore, the choice of vector for gene delivery needs to be carefully considered. Ideally, expression of the therapeutic genes should be subject to physiological regulation and the vector should be able to express the pro-angiogenic genes on demand in response to underlying pathophysiological changes such as tissue hypoxia. Sustainability of the therapeutic effect is another important consideration that is often ignored in the design of clinical trials. All trials, to date, have employed a single administration of the therapeutic gene. However, in all cases, the vectors used (plasmid, adenovirus) express the therapeutic genes only transiently. This may, at least in part, account for the relative lack of success in the trials completed to date. Indeed, evidence from animal studies indicates that angiogenesis is confined to the transient period of transgene expression,[57] and neovessels tend to regress after transgene expression ceases.[58] Thus, successful gene therapy for ischemic diseases may require the use of vectors capable of long-term transgene expression such as AAV, or, at the least, may require multiple treatments. The use of gene therapy for vasculoproliferative diseases also must overcome efficacy issues. The complexity of the pathological process involved in restenosis suggests that genetic manipulation of multiple targets may be necessary for effective and sustained therapeutic benefit. Strategies to accelerate endothelial recovery should also be considered because endothelial damage plays a pivotal role in the subsequent development of restenosis and graft atherosclerosis.

PERSPECTIVES AND FUTURE DIRECTIONS

In the last decade, cardiovascular gene therapy has moved beyond the "proof of concept," into the clinical arena. However, the results from cardiovascular gene therapy trials for tissue ischemia and vessel disease have been disappointing and there is urgent need for further developments in vector and delivery technologies with improved safety and efficacy profiles. The onus is in the development of efficient and nonimmunogenic vector systems capable of conferring tissue-specific expression of therapeutic transgenes in a physiologically regulated fashion. These developments are essential to avert potential ethical and biological hazards such as germ cell line transmission that could arise as a result of nonspecific transgene expression. New delivery devices, together with the new mapping techniques, should also improve the specificity of gene delivery to the areas of interest and minimize systemic spillover. There is a pressing need to define and standardize the protocols for gene transfer in clinical trials. It is also likely that the efficacy of gene therapy for CVD will be enhanced by novel strategies that will allow the simultaneous manipulation of multiple gene targets. We will likely also see an increased reliance on cell-based gene therapy combination strategies for

the treatment of diseases such as coronary artery disease and hind limb ischemia. The field of gene therapy will benefit from developments in genomic research. We envision that genomic profiling will eventually be used for screening and genotyping of patients to detect disease-causing mutations and polymorphisms that should allow the design of individualized genetic therapies.

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Stem Cell Therapy for Cardiovascular Disorders

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The dogma of the heart as an organ composed of terminally-differentiated myocytes incapable of regeneration is being challenged. Evidence has been presented that a fraction of cardiomyocytes is able to reenter the cell-cycle and that limited regeneration can occur after tissue injury through the recruitment of resident and cardiac stem cells.[1] Another idea that has created some excitement is the concept of adult stem cell plasticity.[2,3] Stem cells are capable of self renewal, transformation into dedicated progenitor cells, and differentiation into specialized progeny. Traditionally, adult stem cells were believed to differentiate into progeny only within tissue lineage boundaries (e.g., hematopoietic stem cells giving rise to mature hematopoietic cells). Plasticity implies that stem cells can transdifferentiate into cell types outside their original lineage. In this regard, it has been reported that hematopoietic stem cells, when transplanted into infarcted mouse myocardium, transdifferentiate into cardiomyocytes and vascular cells.[4]

Current cardiovascular therapies are aimed at preventing cell damage and/or progressive functional deterioration after injury. The alleged transdifferentiation capacity of adult stem cells and the discovery of endogenous cardiac repair mechanisms have suggested, for the first time, that cardiac repair might be achieved in the clinical setting.[5] Ironically, although these new ideas have already triggered clinical trials, fusion of transplanted stem cells with resident cardiomyocytes has been offered as an alternative explanation for previous claims of transdifferentiation.[6-9] It has been proposed that stem cells secrete cytokines and growth factors that may promote angiogenesis, suppress cell death of resident cardiomyocytes, or recruit cardiac stem cells (Fig. 3–4).[10-12] Regardless of the mechanisms, there appears to be general agreement that stem cell therapy has the potential to improve perfusion and the contractile performance of the injured heart.[13]

POTENTIAL DONOR CELLS

Conceptually, a variety of stem and progenitor cell populations could be used for cardiac repair. Each cell type has its own profile of advantages, limitations, and practicability issues in specific clinical settings. Studies comparing the regenerative capacity of distinct cell populations are scarce. Many investigators have, therefore, chosen a pragmatic approach by using unfractionated bone marrow cells, which contain different stem and progenitor cell populations, including hematopoietic stem cells, endothelial progenitor cells, and mesenchymal stem cells.

Endothelial Progenitor Cells

Endothelial progenitor cells (EPC) have been defined by their cell surface expression of the hematopoietic marker proteins CD133 and CD34 and the endothelial marker vascular endothelial growth factor receptor-2, and their capacity to incorporate into sites of neovascularization and to differentiate into endothelial cells in situ. The cell surface antigen

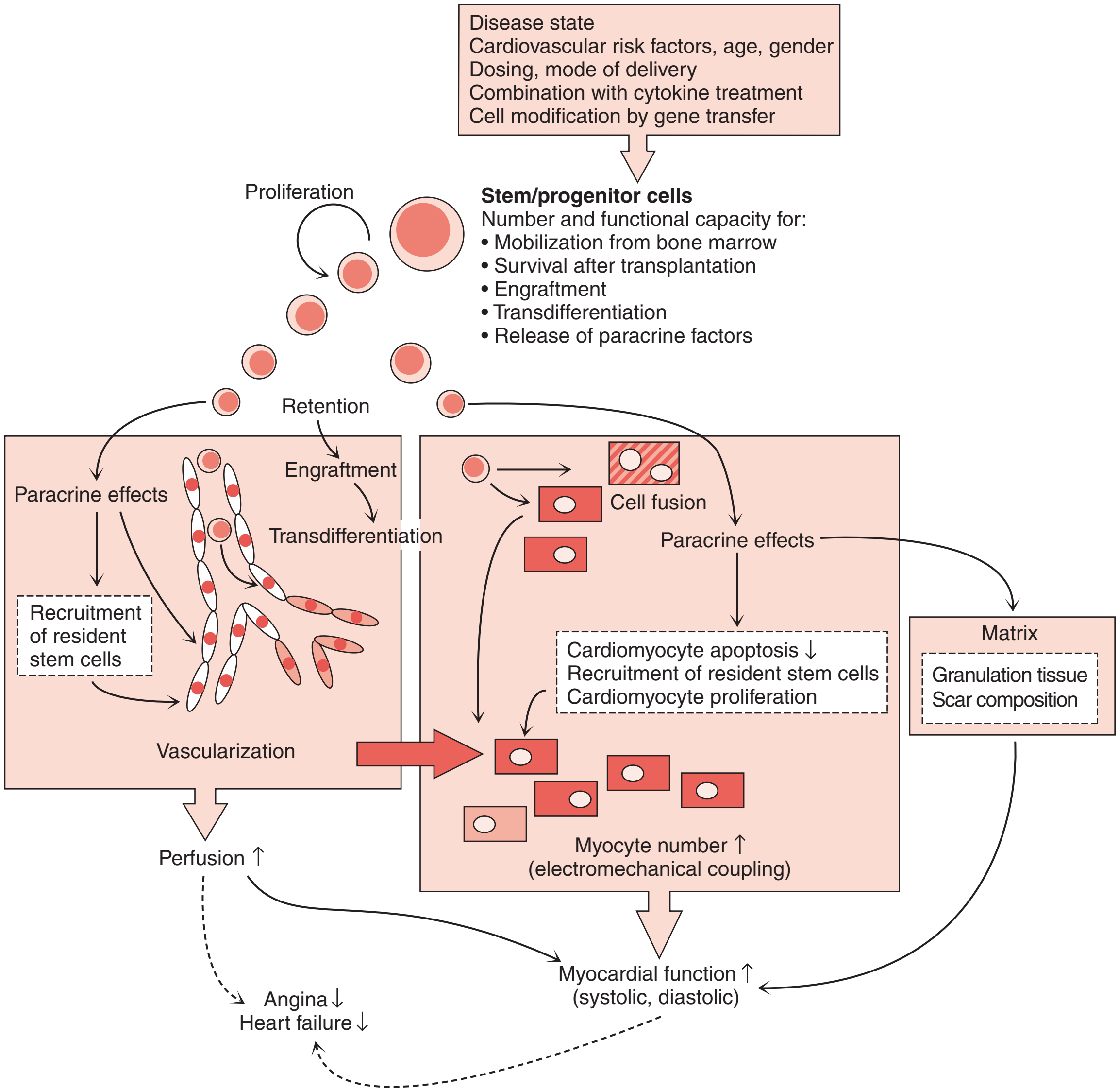

Figure 3–4 Working hypothesis of therapeutic stem cell transplantation for myocardial regeneration. Stem and progenitor cell transplantation can have a favorable impact on tissue perfusion and contractile performance by promoting vascularization and myocyte formation. Improved vascularization may facilitate beneficial effects in the myocyte compartment. Depending on the stem cell type and local milieu, the relative contribution of cell incorporation (transdifferentiation and/or fusion) versus paracrine effects may vary. Stem and progenitor cell numbers and functional capacity are influenced by a patient's age, gender, cardiovascular risk factors, and underlying disease state. (From Wollert KC, Drexler H: Clinical applications of stem cells for the heart. Circ Res 2005;96:151-63.)

CD133 is expressed on early hematopoietic stem cells and endothelial progenitor cells, both of which collaborate to promote vascularization of ischemic tissues. Increasing evidence suggests that culture-expanded EPCs also contain a $CD14^+/CD34^-/CD133^-$-mononuclear cell population with "EPC-capacity," which mediates its angiogenic effects by releasing paracrine factors.[14]

Mesenchymal Stem Cells

Mesenchymal stem cells represent a rare population of $CD34^-$ and $CD133^-$ cells present in bone marrow stroma (10-fold less abundant than hematopoietic stem cells) and other mesenchymal tissues.[15] Mesenchymal stem cells can differentiate into osteocytes, chondrocytes, adipocytes, and cardiomyocyte-like cells under specific culture conditions. When injected into infarct tissue, mesenchymal stem cells may enhance regional wall motion and prevent adverse remodeling.[16,17] It has been suggested that these effects may be related to paracrine effects rather than differentiation of mesenchymal stem cells into cardiomyocytes.[17,18] Because mesenchymal stem cells can be expanded in vitro, and reportedly have a low immunogenicity, they might be used in an allogeneic setting in the future.[15]

Skeletal Myoblasts

Skeletal myoblasts (satellite cells) are progenitor cells that normally lie in a quiescent state under the basal membrane

of mature muscular fibers. Myoblasts can be isolated from skeletal muscle biopsies and expanded in vitro. Myoblasts differentiate into myotubes and retain skeletal muscle properties when transplanted into an infarct scar. Although grafted myotubes may contract in response to electrical stimulation, they do not express intercalated disk proteins, indicating that the majority are not electromechanically coupled to their host cardiomyocytes.[19] Nevertheless, myoblast transplantation has been shown to augment systolic and diastolic performance in animal models of MI, possibly through the release of paracrine factors.[20]

Resident Cardiac Stem Cells

Several groups have detected stem and progenitor cells within the heart that are capable of differentiating into cardiomyocytes and/or vascular lineages. It has been suggested that these cells could be clonally expanded and be used for cardiac repair in an autologous setting.[21-25] Intriguingly, different groups have used distinct surface markers to characterize resident cardiac stem cells, although it is not clear yet whether this reflects the presence of distinct stem cell populations or only different stages in the evolution of a common cell type. In any case, cardiac resident stem and progenitor cells hold great promise for clinical applications, although, it is conceivable that the bone marrow may contain a cardiogenic, pluripotent stem cell population with similar properties.[26,27]

Embryonic Stem Cells

Embryonic stem cells are totipotent stem cells derived from the inner cell mass of blastocysts. Under specific culture conditions, embryonic stem cells differentiate into multicellular embryoid bodies that contain differentiated cells from all three germ layers including cardiomyocytes. Human embryonic stem cell–derived cardiomyocytes display structural and functional properties of early-stage cardiomyocytes that couple with host cardiomyocytes when transplanted into normal or infarcted myocardium.[28,29] In theory, infinite numbers of cardiomyocytes could be obtained from human embryonic stem cell clones. However, unresolved ethical and legal issues, concerns about the tumorigenicity of the cells, and the need to use allogeneic cells for transplantation currently hamper their use in clinical studies. Eventually, nuclear transfer techniques may provide a means for generating an unlimited supply of histocompatible embryonic stem cells for the treatment of cardiac disease (therapeutic cloning).

MODES OF CELL DELIVERY

The goal of any cell delivery strategy is to transplant sufficient numbers of cells into the myocardial region of interest and to achieve maximum retention of cells within that area. Retention may be defined as the fraction of transplanted cells retained in the myocardium for a short period of time (hours). The local milieu is an important determinant of cell retention because it will influence short-term cell survival and, if a transvascular approach is used, cell adhesion, transmigration through the vascular wall, and tissue invasion.

Transvascular Approaches

Transvascular strategies are especially suited for the treatment of recently infarcted and reperfused myocardium when chemoattractants are highly expressed.[30]

Intracoronary Artery Infusion

Selective intracoronary application delivers a maximum concentration of cells homogeneously to the site of injury. Unselected bone marrow cells, circulating blood-derived progenitors cells, and mesenchymal stem cells have been delivered via the intracoronary route in patients with acute myocardial infarction (AMI) and ischemic cardiomyopathy. In these studies, cells were delivered through the central lumen of an over-the-wire balloon catheter during transient balloon inflations to maximize the contact time of the cells with the microcirculation of the infarct-related artery.[31]

Intravenous Infusion

In experimental models, intravenous delivery of endothelial progenitors cells and mesenchymal stem cells has been shown to improve cardiac function after AMI. However, cell homing to noncardiac organs limits the applicability of this approach.[32,33] Indeed, in a clinical study, homing of unselected bone marrow cells to the infarct region was observed only after intracoronary stop-flow delivery but not after intravenous infusion.[34]

Mobilization of Stem and Progenitor Cells

Considering that the acutely infarcted myocardium recruits circulating stem and progenitor cells to the site of injury, mobilization of stem and progenitor cells by cytokines may offer a noninvasive strategy for cardiac regeneration. Indeed, it has been reported that the stem cell mobilizing cytokine stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) improve cardiac function after AMI in mice.[35,36] Notably, G-CSF can accelerate infarct healing by enhancing macrophage infiltration and matrix metalloproteinase activation and suppressing cardiomyocyte apoptosis by activating the cytoprotective STAT3 transcription factor, suggesting that stem cell independent mechanisms may contribute to the favorable effects of G-CSF post-AMI.[37,38]

Direct Injection in the Ventricular Wall

Direct injection is the preferred route for cell delivery in patients who present late in the disease process, when an occluded coronary artery precludes transvascular cell delivery (patients with chronic myocardial ischemia) or when cell homing signals are expressed at low levels in the heart (scar tissue). However, direct injection of cells into ischemic or scarred myocardium may create islands of cells with limited blood supply and lead to poor cell survival. Direct injection techniques are especially suited for the application of large cells, such as mesenchymal stem cells or myoblasts that may

cause microembolization after intracoronary delivery. Cell delivery by direct injection may not be safe in patients with a recent MI, particularly if cells are to be injected into the friable necrotic tissue.

Transepicardial Injection

Transepicardial cell injection has been performed as an adjunct to coronary artery bypass grafting. Transepicardial cell injection during open heart surgery allows for a direct visualization of the myocardium and a targeted application of cells. The invasiveness of this approach hampers its use as a stand-alone therapy. Conversely, the efficiency of cell transplantation may be difficult to ascertain if bypass grafting is performed simultaneously.

Transendocardial Injection

Using an injection needle catheter advanced across the aortic valve and positioned against the endocardial surface, cells can be directly injected into the left ventricular wall.[39] Electromechanical mapping of the endocardial surface can be used to delineate viable, ischemic, and scarred myocardium before cell injections.

Transcoronary Vein Injection

A catheter system incorporating an ultrasound tip for guidance and an extendable needle for myocardial access can be used to deliver cells through the coronary veins into the myocardium.[40] In contrast to the transendocardial approach, where cells are injected perpendicular to the ventricular wall, the composite catheter system delivers cells parallel to the ventricular wall and deep into the injured myocardium. However, positioning of the injection catheter in a specific coronary vein is not trivial in all cases.

CLINICAL APPLICATIONS OF STEM CELL THERAPY

Myocardial Infarction

Modern reperfusion strategies and advances in pharmacological management have resulted in an increasing proportion of MI survivors who are at heightened risk of developing adverse left ventricular remodeling and heart failure. None of our current therapies addresses the underlying cause of the remodeling process, i.e., the damage of cardiomyocytes and the vasculature in the infarcted area.

Clinical Trial Experience

Inspired by experimental data suggesting that functional recovery after MI can be augmented by stem cell transfer,[4,9,10,41,42] several trials were initiated to assess the therapeutic potential of cell therapy in patients post-MI. All clinical studies included patients who had undergone primary angioplasty and stent implantation to reopen the infarct-related artery and who received optimal medical treatment during the acute phase and follow-up. Cells were infused intracoronarily by using the stop-flow balloon catheter approach. Current trials may be categorized into studies that use unselected bone marrow cells or selected stem cell populations.

Unselected Bone Marrow Cells

Following three initial safety and feasibility studies,[31,43,44] four larger randomized trials of bone marrow cell therapy after MI have been completed (Table 3–4).[45-48] The combined experience from these trials indicates that intracoronary delivery of unselected bone marrow cells is feasible and safe in the short- and mid-term (up to 18 months).[49,50] Bone marrow harvest and intracoronary cell delivery are not associated

Table 3–4 Randomized Cell Therapy Trials in Patients with Acute Myocardial Infarction

Study	Design	[*n*]	Cell Type	Dose	Time of Delivery Post-AMI	Outcomes	
						Improved	No Change
BOOST[45]	Randomized-controlled	30 Treated 30 Controls	Nucleated BMCs	128 mL	6 ± 1 days	Global LVEF	LVEDV
REPAIR-AMI[46]	Placebo-controlled	95 Treated 92 Controls	Mononucleated BMCs	50 mL	3-6 days	Global LVEF	LVEDV
Janssens[47] et al.	Placebo-controlled	32 Treated 34 Controls	Mononucleated BMCs	130 mL	1 day	—	Global LVEF LVEDV
ASTAMI[48]	Randomized-controlled	47 Treated 50 Controls	Lymphocytic BMCs	50 mL	6 ± 1 days	—	Global LVEF LVEDV

In BOOST, cells were prepared by gelatin-polysuccinate density gradient sedimentation, which retrieves all nucleated cell types from the bone marrow; REPAIR-AMI and Janssens et al. employed a Ficoll gradient, which recovers the mononuclear cell fraction. In ASTAMI, lymphocytic bone marrow cells were enriched by using the Lymphoprep solution. Dose refers to the average amount of bone marrow that was harvested. AMI, acute myocardial infarction; BMC, bone marrow cell; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.

with bleeding complications or ischemic damage to the myocardium. No increased rates of in-stent restenosis have been observed after cell transfer. Clinical surveillance, ambulatory ECG monitoring, and data from an electrophysiological study indicate that bone marrow cell transfer is not associated with an increased propensity to ventricular arrhythmias; moreover, intramyocardial calcifications or tumor formation were not observed after intracoronary bone marrow cell delivery.[45,49,50]

In the BOne marrOw transfer to enhance ST-elevation infarct regeneration (BOOST) trial, intracoronary transfer of nucleated bone marrow cells resulted in an improvement of global left ventricular ejection fraction of 6 percentage points after 6 months compared with the control group. This improvement of ejection fraction was due mostly to improved regional wall motion in the infarct border zone.[45] For comparison, improvements of 3 to 4 percentage points are achieved by primary angioplasty and stent implantation in MI, suggesting that the further improvement of ejection fraction by cell therapy may be clinically meaningful.[51,52]

The beneficial effects of intracoronary bone marrow cell transfer were confirmed in the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial. In this study, mononucleated bone marrow cell transfer promoted an increase in left ventricular ejection fraction of 2.5 percentage points after 4 months compared with a control group that also underwent bone marrow aspiration but received an intracoronary infusion of a placebo.[46]

In contrast to BOOST and REPAIR-AMI, two other randomized studies did not report significant improvements of left ventricular ejection fraction after intracoronary cell transfer.[47,48] The exact reasons for the differing results remain elusive, and it is worthwhile to take a closer look at the design of these studies (see Table 3–4). In one of the negative studies, cells were delivered very early after coronary reperfusion (i.e., already after 24 hours.)[47] In BOOST and REPAIR-AMI, cells were transplanted several days later. Subgroup analyses in REPAIR-AMI indicate that the timing of cell delivery may be very important, and that the beneficial effects on ejection fraction may be lost when the cells are delivered too early. The Autologous Stem cell Transplantation in Acute Myocardial Infarction (ASTAMI) trial also did not find a significant effect of bone marrow cell transfer on left ventricular ejection fraction recovery.[48] Although the cells were delivered late in ASTAMI (i.e., after 4 to 6 days) a particular cell preparation method that leads to an enrichment of lymphocytic bone marrow cells was employed. It is not clear whether this method actually recovers the bone marrow cell populations that are required to achieve functional improvements after MI. Together, these data remind us that procedural issues, such as the cell preparation method and timing of cell transfer, need to be addressed in future studies.

None of the trials has revealed a significant effect of bone marrow cell transfer on left ventricular end-diastolic volumes, an index of left ventricular remodeling. However, larger studies may be required to settle this issue. Moreover, little data are available regarding the long-term effects of bone marrow cell transfer after MI. Follow-up data from the BOOST trial indicate that the improvements of left ventricular ejection fraction are maintained 18 months after cell transfer; however, ejection fraction also increased somewhat in the control group during long-term follow-up. Analysis of the time course of left ventricular functional improvement indicates that left ventricular ejection fraction recovery occurs significantly faster in the cell transfer group compared with the control group.[50] Tissue Doppler echocardiography analyses in BOOST indicate that bone marrow cell transfer may prevent the development of diastolic dysfunction during long-term follow-up. Significant effects of cell transfer on E/A ratio and tissue Doppler Ea/Aa ratio, but not on isovolumic relaxation time (IVRT), suggest that cell therapy positively affects left ventricular stiffness but not active relaxation.[53]

Selected Bone Marrow Cell Populations

The Transplantation Of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial compared mononucleated bone marrow cells with circulating blood-derived progenitor cells (mostly endothelial progenitor cells). Both cell types appeared to have similar safety and efficacy profiles.[49] However, because TOPCARE-AMI was not randomized, firm conclusions regarding the efficacy of endothelial progenitor cells post-MI cannot be drawn at the present time. The effects of culture-expanded mesenchymal stem cells after MI have been investigated in one randomized clinical trial.[54] Although no serious side effects were reported, it is not known whether intracoronary mesenchymal stem cell delivery promoted ischemic damage to the myocardium,[54] a complication that has occurred after intracoronary mesenchymal stem cell infusions in dogs.[55] Six months after cell transfer, regional wall motion and global left ventricular ejection fraction were improved and left ventricular end-diastolic volumes were decreased.[54] These striking effects need to be confirmed by additional studies. In another trial, $CD133^+$ bone marrow cells were infused into the infarct-related artery.[56,57] After 4 months, 6 out of 14 patients had developed in-stent restenosis, and two had developed de novo lesions in the infarct-related artery.[57] These numbers are worrisome; however, the study may be too small to establish a causal relation with $CD133^+$ cell transfer. Although left ventricular ejection fraction increased after $CD133^+$ cell transfer, reliable conclusions regarding efficacy cannot be derived from this small pilot trial.[56]

Stem and Progenitor Cell Mobilization

Data from an initial pilot study suggested that G-CSF may increase the risk of in-stent restenosis in patients with myocardial infarction.[58] This trial, however, has received much criticism, mostly because balloon angioplasty and stenting were delayed until after the course of G-CSF had been completed. G-CSF has the potential to promote neutrophil recruitment to sites of inflammation and tissue injury,[59] which may have contributed to excess neointima proliferation and restenosis in this study. The Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Use of Granulocyte-Colony-Stimulating Factor (FIRSTLINE-AMI) trial randomized 50 patients with MI to a control group or a 6-day open-label course of G-CSF that was initiated within 1 to 2 hours after primary angioplasty and stenting.[60] G-CSF therapy after stent implantation was not associated with an enhanced rate of in-stent restenosis or other serious adverse events and promoted significant improvements in left ventricular ejection fraction and metabolic activity in the infarct territory.[60]

Critics have pointed out that the beneficial effects of G-CSF in FIRSTLINE-AMI were magnified by an unexpected decrease in ejection fraction in the control group.[61] The favorable safety profile of G-CSF post-MI was confirmed in another trial that included 20 patients; this trial did not, however, observe a beneficial effect on left ventricular ejection fraction.[62] Similarly, a randomized-controlled study that involved 114 patients with AMI did not find a significant effect of G-CSF on left ventricular ejection fraction recovery.[63] It remains to be seen whether subtle differences in study design (e.g., the timing of G-CSF application after MI) might account for these discrepant results.

CORONARY ARTERY DISEASE WITH NO MECHANICAL REVASCULARIZATION OPTION

Despite significant advances in coronary revascularization techniques, some patients with coronary artery disease have no revascularization option due to the diffuse nature of their disease. Some of these patients experience anginal symptoms despite maximal medical therapy. Chronic myocardial ischemia can be associated with a regional impairment of contractile function that is partially reversible when tissue perfusion is restored (hibernating myocardium), emphasizing that there is a need for therapeutic strategies aimed at delivering oxygenated blood to the myocardium in these patients. Intramyocardial injection of bone marrow cells or endothelial progenitor cells enhances collateral flow, capillary density, and regional contractility in animal models of chronic myocardial ischemia.[42,64] Because stem and progenitor cells may deliver a natural cocktail of angiogenic and arteriogenic cytokines to the myocardium,[12,64-66] it is conceivable that cell therapy may have advantages above single-cytokine gene therapy approaches to treat myocardial ischemia.[67]

Clinical Trial Experience

Unselected mononuclear bone marrow cells have been used in several small-scale studies in patients with coronary artery disease that is not amenable to conventional revascularization techniques (Table 3–5). Cells were injected into the ischemic myocardium either transepicardially during coronary artery bypass grafting or transendocardially under electromechanical guidance.[39,65,68,69] Together, these early studies suggest that intramyocardial bone marrow cell injections are feasible and, possibly, safe in these patients. Although improvements of anginal symptoms, exercise capacity, regional tissue perfusion, and regional left ventricular systolic function were observed in these studies, firm conclusions regarding efficacy cannot be drawn because of the size and nonrandomized nature of these reports. The experience with transmyocardial laser revascularization has highlighted the need for blinded control groups to control for the placebo effect typically observed in this patient population.[70] Still, the idea to improve myocardial perfusion by bone marrow cell injections is intriguing and should be tested prospectively in larger, randomized clinical trials.

The effects of G-CSF on symptoms and myocardial perfusion has been investigated in 16 patients with intractable angina.[71] Although G-CSF promoted a strong increase in circulating endothelial progenitor cell numbers, there was no evidence of enhanced myocardial perfusion or improved regional wall motion. Furthermore, two patients suffered MIs, raising concerns about the safety of G-CSF in this patient population.[71] Any future trials investigating the role of G-CSF in such patients should employ a careful dose-escalating regimen. However, a serious limitation of any stem cell mobilizing strategy in this patient population may be that circulating cells have insufficient access to the ischemic myocardium.

ISCHEMIC CARDIOMYOPATHY, CHRONIC HEART FAILURE

Chronic heart failure has emerged as a major worldwide epidemic. A fundamental shift in the underlying etiology is becoming evident, in which the most common cause of heart failure is no longer hypertension or valvular disease, but rather long-term survival after MI.[72] Conceptually, replacement of akinetic scar tissue by viable myocardium should improve cardiac function and impede progressive LV remodeling. However, among various potential indications for stem cell therapy, repair of scar tissue may be the most challenging. Transplanted cells will face limited blood supply and may not receive the environmental cues essential for differentiation into vascular cells or cardiomyocytes.

Table 3–5 Non-Randomized Cell Therapy Trials in Patients with Myocardial Ischemia and No Revascularization Option

Study	[*n*]	LVEF	Cell Type	Delivery	Reported Outcomes
Hamano et al[68]	5 Treated No controls	–	Mononucleated BMCs	Transepicardial (during CABG)	Regional perfusion ↑
Tse et al[69]	8 Treated No controls	58 ± 11%	Mononucleated BMCs	Transendocardial (guided by EMM)	Regional perfusion ↑ Regional wall motion ↑
Fuchs et al[65]	10 Treated No controls	47 ± 10%	Nucleated BMCs	Transendocardial (guided by EMM)	Regional perfusion ↑
Perin et al[39]	14 Treated 7 Controls	30 ± 6%	Mononucleated BMCs	Transendocardial (guided by EMM)	Regional perfusion ↑ Regional wall motion ↑

BMC, bone marrow cell; CABG, coronary artery bypass grafting; EMM, electromechanical mapping; LVEF, baseline left ventricular ejection fraction.

Clinical Trial Experience

Skeletal Myoblasts

Following an initial case report,[73] several small trials investigating the safety and feasibility of myoblast transplantation in patients with ischemic cardiomyopathy have been published.[40,74-79] Cells were injected either transepicardially during coronary artery bypass grafting or transendocardially guided by electromechanical mapping (Table 3–6). One major safety concern has arisen from these studies, that is, that myoblast grafts may represent an arrhythmogenic substrate, especially early after cell injection.[80] Concerning the mechanisms of such proarrhythmic effects, it has been proposed that some transplanted myoblasts fuse with cardiomyocytes, thereby generating spatial heterogeneity of Ca^{2+} signaling at the graft-host interface.[81] Moreover, tissue injury and local inflammation could play roles.[74,82] In most trials, improvements of regional wall motion, global left ventricular ejection fraction, and/or tissue viability have been reported after myoblast injections. However, owing to the small number of patients, lack of control groups, and the confounding effect of concomitant revascularization, meaningful conclusions regarding efficacy cannot be drawn at this time.

Table 3–6 Non-Randomized Cell Therapy Trials in Patients with Ischemic Cardiomyopathy

Study	[*n*]	LVEF	Cell Type	Time after MI	Delivery	Reported Outcomes
Menasche et al[74]	10 Treated No controls	24 ± 4%	Myoblasts	3-228 Mo	Transepicardial (during CABG)	Regional wall motion ↑ Global LVEF ↑
Herreros et al[75]	11 Treated No controls	36 ± 8%	Myoblasts	3-168 Mo	Transepicardial (during CABG)	Regional wall motion ↑ Global LVEF ↑ Viability in infarct area ↑
Siminiak et al[76]	10 Treated No controls	25-40%	Myoblasts	4-108 Mo	Transepicardial (during CABG)	Regional wall motion ↑ Global LVEF ↑
Chachques et al[77]	20 Treated No controls	28 ± 3%	Myoblasts	Not reported	Transepicardial (during CABG)	Regional wall motion ↑ Global LVEF ↑ Viability in infarct area ↑
Smits et al[78]	5 Treated No controls	36 ± 11%	Myoblasts	24-132 Mo	Transendocardial (guided by EMM)	Regional wall motion ↑ Global LVEF ↑
Siminiak et al[40]	10 Treated No controls	30-51%	Myoblasts	5-96 Mo	Transendocardial (guided by EMM)	Global LVEF ↑
Dib et al[79]	24 Treated No controls	15-43%	Myoblasts	not reported	Transepicardial (during CABG)	Global LVEF ↑ Viability in infarct area ↑
Stamm et al[83,84]	12 Treated No controls	36 ± 11%	$CD133^+$	3-12 Wk	Transepicardial (during CABG)	Global LVEF ↑ perfusion ↑
Strauer et al[86]	18 Treated 18 Controls	52 ± 9%	Mononucleated BMCs	5-102 Mo	Intracoronary	Regional wall motion ↑ Global LVEF ↑ Viability in infarct area ↑
Assmus et al[85]	73 Treated 23 Controls	40±11%	Mononucleated BMCs Circulating progenitor cells	3-358 Mo	Intracoronary	GLobal LVEF ↑ (only in BMC group)

LVEF denotes left ventricular ejection fraction; $CD133^+$, bone marrow–derived CD133 positive cells; BMC, bone marrow cell; MI, myocardial infarction; CABG, coronary artery bypass grafting; EMM, electromechanical mapping, LVEF, left ventricular ejection fraction.

Bone Marrow Cells

In another pilot study, $CD133^+$ bone marrow cells were injected transepicardially into the infarct border zone in patients undergoing bypass grafting of noninjected myocardial areas (see Table 3–6).[83,84] No procedure-related complications or serious ventricular arrhythmias were observed. After 6 months, perfusion of the cell-injected area and global left ventricular ejection fraction were improved. However, because there was no control group, the efficacy of this approach remains uncertain. In two other trials, patients with ischemic cardiomyopathy were treated with unselected mononucleated bone marrow cells, using the stop-flow balloon catheter technique.[85,86] Similar to patients with MI, the procedure appeared to be safe. Significant improvements of left ventricular ejection fraction were reported in both trials. Notably, one of these studies also included a group of patients receiving an intracoronary infusion of circulating blood-derived progenitor cells; treatment with these cells did not promote improvements of left ventricular systolic function.[85]

THE FORESEEABLE FUTURE OF CARDIOVASCULAR STEM CELL THERAPY

A flurry of small, mostly uncontrolled clinical studies exploring the safety and feasibility of stem cell therapy have been conducted. These studies have used numerous different cell types and preparations, each in a small number of patients with different disease states. Although these clinical studies have generated a great deal of hope, we should take into account the lessons learned from the translation of therapeutic angiogenesis into clinical studies, where great expectations raised by open studies have not been confirmed by subsequent randomized trials. We advocate to no longer perform studies involving small numbers of patients, but rather to conduct intermediate-sized, double-blind, randomized controlled clinical trials to establish the effects of stem cell therapy on surrogate markers, such as left ventricular ejection fraction, myocardial perfusion, or exercise capacity. Upcoming trials should address procedural issues such as the optimal cell type, cell dosage, and timing of cell transfer. These trials may also look at combined morbidity and mortality endpoints, although they may be too small to be conclusive in this regard. Ultimately, outcome trials will have to be conducted.

Notably, the absolute number of transplanted cells did not correlate with subsequent improvements in ejection fraction in previous post-MI studies.[45,87] This may be because the cell numbers infused were within a narrow range, or because of differences in the functional capacity of the cells, such as the ability to home to and engraft in the infarcted area, to undergo transdifferentiation and/or to produce paracrine factors, may override differences in cell numbers. Intriguingly, cell labeling studies indicate that less than 5% of unselected nucleated bone marrow cells are retained in the infarcted area after intracoronary delivery in patients (Fig. 3–5).[34] Although this rate of cell retention was sufficient to improve left ventricular systolic and diastolic function in the BOOST trial,[45,53] it is conceivable that pharmacologic strategies might be used to enhance the homing capacity or other functional parameters

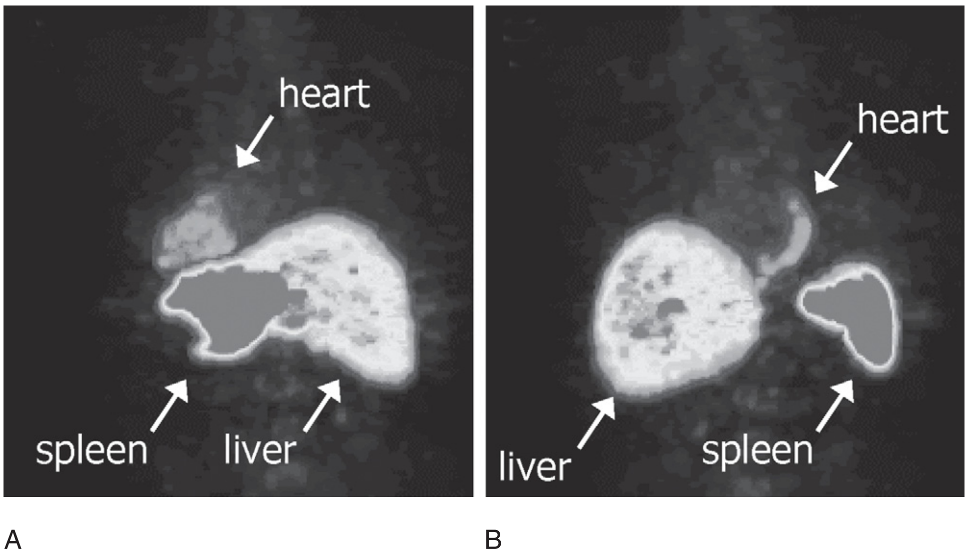

Figure 3–5 (*See also Color Plate 3–5.*) Myocardial homing and biodistribution of ^{18}F-FDG-labeled bone marrow cells after intracoronary transfer. Nine days after primary balloon angioplasty and stent implantation for an acute ST-segment myocardial infarction, this patient received an intracoronary infusion of autologous nucleated bone marrow cells into the stented left circumflex coronary artery. A small fraction of the cells was radiolabeled with 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) just before intracoronary transfer. Positron emission tomography imaging was performed 65 minutes after cell transfer. Left posterior oblique (**A**) and left anterior oblique (**B**) views of the chest and upper abdomen are shown. Approximately 3% of the cells homed to the lateral wall of the heart; most remaining activity is detected in the liver and spleen. (From Hofmann M, Wollert KC, Meyer GP, et al: Monitoring of bone marrow cell homing into the infarcted human myocardium. Circulation 2005;111:2198-2202.)

of the cells. Post-hoc analyses of the BOOST trial database suggest that the effects of bone marrow cell transfer are consistent across several subgroups defined according to sex, age, infarct territory, and time from symptom onset to reperfusion.[45] However, patient subgroups that derive the greatest benefit from cell transfer need to be identified prospectively in future trials (e.g., patients presenting late after symptom onset in whom little myocardial salvage can be expected from reperfusion therapy). In this regard, data from REPAIR-AMI indicate that the effects of bone marrow cell transfer may be more pronounced in patients with more severely depressed baseline left ventricular ejection fraction.[46] G-CSF or other cytokines with stem-cell mobilizing and/or direct cardioprotective properties[88,89] should be further evaluated as stand alone therapy or in combination with cell transfer after MI. Cytokines might evolve as a noninvasive alternative or as an adjunct to cell therapy.

Randomized, double-blind trials with sufficient statistical power are needed to rigorously evaluate the safety and efficacy of myoblasts and other cell types in patients with ischemic heart failure. It may be advisable to restrict the use of myoblast transplantation to patients with an implantable cardioverter-defibrillator. The monitoring function of the ICD will provide critical information on the natural course of myoblast-induced arrhythmias. Post-mortem studies indicate that only a small fraction of injected myoblasts survive in scarred human myocardium.[90,91] Accordingly, preimplantation anti-apoptotic treatments or co-injection of angiogenic growth factors may enhance myoblast survival after transplantation. Another strategy may involve the ectopic expression of connexin 43 in myoblasts, which may permit electrical coupling with resident cardiomyocytes.[92,93] Considering that functional benefits of cell transplantation have been observed in animals with dilated cardiomyopathy,[94] future trials may also want to explore the role of cell therapy in patients with nonischemic heart failure.

Meanwhile, fundamental questions need to be addressed experimentally. What is the fate of the injected cells after transplantation? How long do they survive? Do the cells incorporate, or is transient retention sufficient to promote functional effects? Genetic and transgenic markers should be employed to determine the lineage commitment of engrafted cells. Cell labeling and imaging techniques need to be developed to track stem cell fate in patients and correlate cell retention and engraftment with functional outcomes. Emerging evidence suggests that transplanted cells may interact with resident cardiac stem cells to enhance their regenerative potential. What is the nature and functional relevance of this interaction? Can the regenerative capacity of transplanted stem cells be enhanced by drugs, cytokines, or gene therapy approaches? Pharmacologic and genetic strategies may help to enhance stem cell retention, engraftment, differentiation, and paracrine capability.[16,95-97] The “holy grail” of cell therapy is the replacement of necrotic or scarred myocardial tissue with functional myocytes receiving sufficient blood supply. Although the cell types that have been tested in clinical trials so far (e.g., bone marrow cells, myoblasts) may have a favorable impact on systolic function, they probably do not make new myocardium. This should stimulate further basic research into the prospects of cell types with transdifferentiation capacity, such as ES-cells, resident cardiac stem cells, or multipotent bone marrow-derived stem cells.

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Chapter 4

The Process of Regulatory Review for New Cardiovascular Devices*

Neal I. Muni and Bram D. Zuckerman

CHAPTER CONTENTS

Cardiovascular device development has advanced significantly over the last decade, with a remarkable increase in the variety and complexity of available devices and diagnostic tests for cardiac illnesses. Assessment of cardiovascular safety and effectiveness is a challenging, multidimensional task with many groups having important roles in the process. As the key regulatory agency assigned to review and approve of devices in the United States, the Food and Drug Administration's Center for Devices and Radiological Health (CDRH) has an essential, but not exclusive, role in bringing new medical devices to market. It is vital that the FDA effectively interact with the clinical community, industry, and the public at every stage of the medical device life cycle to make the necessary risk and benefit decisions to assist in device development.

This chapter will provide an introduction to the process of regulatory review of new cardiovascular devices, including special challenges faced in the regulation of device treatments as compared with drugs. The chapter will also focus on the evolution of the device regulatory process over the last 10 years, and will include special topics of interest to the practicing physician, including "off-label" use of cardiovascular devices, as well as the responsibilities of cardiologists to ensure the safety and effectiveness of device therapies.

REGULATORY HISTORY OF THE DEVICE REVIEW PROCESS

Although medical devices have been regulated by the U.S. Government since passage of the Federal Food, Drug, and Cosmetic Act ("the Act") in 1938, the FDA's authority was limited to identifying and taking action against sham devices, including pulling them from the market. Over the next 40 years, however, the limitations of this approach became apparent with the growing complexity of device technology and the identification of major safety-related problems with higher-risk medical devices, such as pacemakers and heart valves. As a result of this increased recognition of device complexity and safety concerns, the U.S. Congress, with the assistance of independent medical experts, thoroughly reviewed the existing device laws and initiated a change to the FDA's regulatory mandate for medical devices. Congress understood the importance of fostering continued technological innovation but with improved safeguards to protect the public from an unreasonable level of risk.[1] With passage of the Medical Device Amendments to the Act in 1976, the FDA was formally given the authority to assess device safety and effectiveness as a precondition for marketing approval.

As basically defined by the Act, devices are (1) instruments, apparatus, implants, or in vitro reagents intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease or condition; and/or (2) intended to affect the structure or any function of the body that does not achieve its intended use through chemical action and that is not dependent on being metabolized for the achievement of its primary intended purposes.[†] Approaches to clinical evaluation and review of medical devices must take into consideration the diagnostic or therapeutic use for which the device is intended, the technological characteristics of the device, and the level of potential risk inherent to the device.

The Medical Device Classification System

The medical device classification system is a risk-based classification scheme. It forms the basis of the FDA device review process and is unique to devices; drug evaluation does not have a parallel classification system and instead, uses a more uniform process. The Medical Device Amendments of 1976 created three separate classification levels for medical devices based on the device's level of clinical risk. Class I represents a minimal risk device whose safety and effectiveness is well established. Class II devices represent intermediate risk and often require "special controls" such as labeling to ensure safe and effective use. Class III devices are devices of significant risk, with the assessment of risk based not only

*This chapter represents the professional opinions of the authors and is not an official document, agency guidance, or policy of the U.S. Government, the Department of Health and Human Services, or the Food and Drug Administration, nor should any official endorsement be inferred.

†FDC Act" 21 U.S.C. § 201(h).

on the characteristics of the device but also the likelihood of associated morbidity or mortality. Examples of class III cardiovascular devices include most implantable devices, such as intracoronary stents, cardiac pacemakers, and left ventricular assist devices. Other devices, including cardiac diagnostic equipment such as computerized electrocardiographic devices are considered to be intermediate risk (class II).[2] Class I devices are considered of minimal risk and are exempt from pre-market review if they are for the same use as and composed of the same technology as other legally marketed devices. A cardiovascular class I device example is a cardiac chair, designed for proper posture for cardiac and pulmonary treatment.

Any device that was in commercial distribution before the passage of the 1976 Medical Device Amendments is considered a *preamendment* device, and was effectively "grandfathered," being assigned to the least-regulated class that allowed a reasonable assurance of safety and effectiveness. Unless the FDA has taken specific regulatory action to reclassify a preamendment device, it is allowed to remain on the market.

Pathways for Regulatory Review of Cardiovascular Devices

The first step in the device evaluation process is to determine the classification level of the device based on its regulatory requirements. Based on the classification of the device, a medical device manufacturer would usually take either of two key regulatory pathways, the "510(k)" pre-market notification submission, or submission of a pre-market approval (PMA) application, demonstrated in Figure 4–1.

510(k) Pre-market Notification

The 1976 Medical Device Amendments added a pre-market notification provision to Section 510 of the Food, Drug, and Cosmetic Act (section 510[k]), requiring that each firm register its manufacturing facility with the FDA and submit a 510(k) for pre-market review. The first step in the 510(k) evaluation process is to compare the device with existing, marketed class I or II devices (called *predicate* devices) in terms of their intended use, technology, and performance. If the new device can be demonstrated to be *substantially equivalent* to the predicate device, that it is at least as safe and effective, it is cleared for marketing by the FDA. The FDA has a statutory requirement of 90 days to review and make a marketing clearance determination. The manufacturer must receive a letter from the FDA allowing it to market the device before commercial distribution of the device in the United States.

The majority of medical devices cleared for marketing in the United States have done so via the 510(k) pre-market

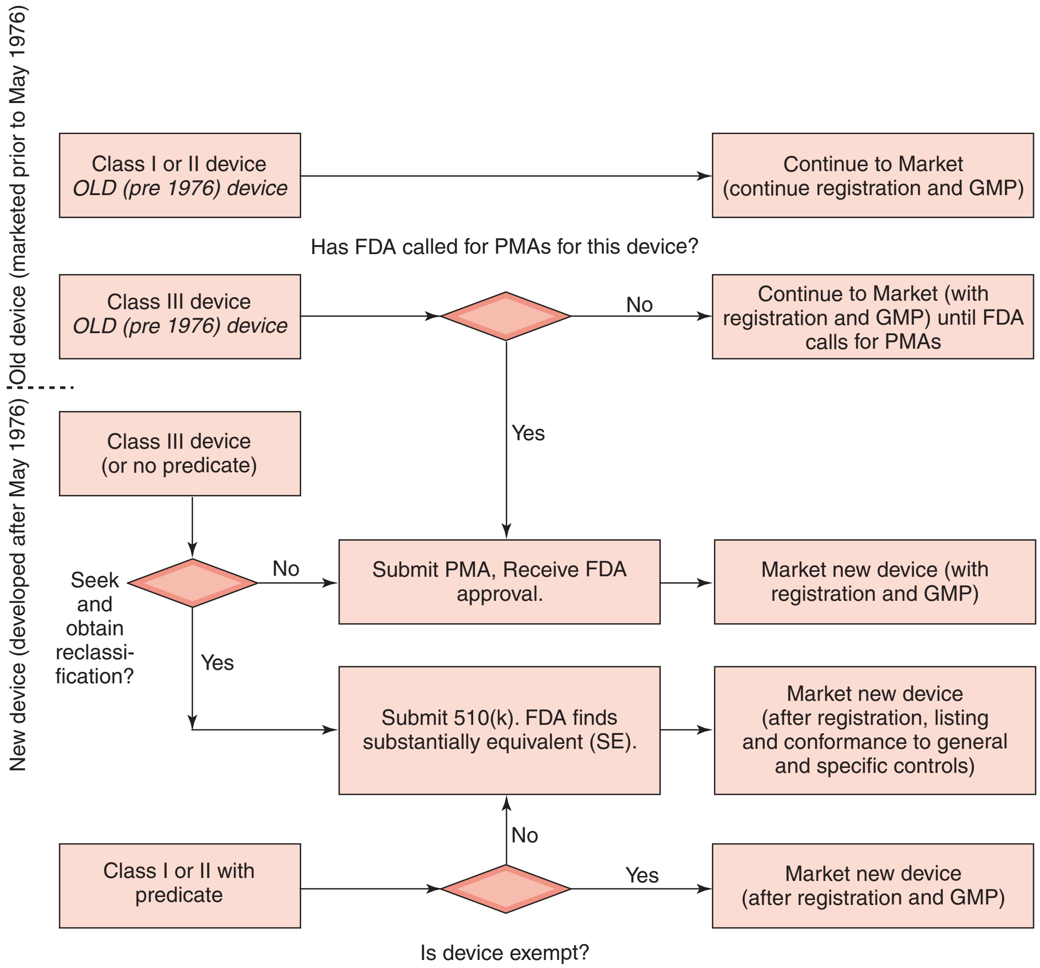

Figure 4–1 Pathways for Regulatory Marketing Clearance and Approval. (Redrawn from the U.S. Food and Drug Administration.)

notification process. As an example, in 2004, a total of 3635 original 510(k) pre-market notifications were received by the Agency, compared with 54 original PMA applications.[3] Approximately 10% to 15% of 510(k) submissions contain clinical performance data. As an example, noninvasive blood pressure (NIBP) cuffs are considered intermediate risk, or class II, devices. Whereas new NIBP devices require appropriate validation by bench and clinical testing, a modification to a previously cleared NIBP device may not need revalidation with clinical testing, depending on the nature of the change, unless the manufacturer plans to market it with a new indication for use or a new fundamental technology. However, other cardiovascular devices classified as class II devices, such as intravascular embolic protection devices, do require clinical performance assessments to make the determination of substantial equivalence.

Pre-market Approval Application

In contrast to class I and II devices that undergo the 510(k) review process, marketing review for higher risk, class III devices must undergo the Pre-Market Approval (PMA) regulatory pathway.* The PMA pathway applies to devices that: (1) are life sustaining or supporting; (2) are of substantial importance in preventing the impairment of human health; and (3) present a potential unreasonable risk of illness or injury.[2 *]

As a condition for FDA approval of a PMA application, a manufacturer must demonstrate a reasonable assurance of the *safety and effectiveness* of a device with respect to its indications for use. For cardiovascular devices classified as class III devices, such as pacemakers, intracoronary stents, and circulatory support devices, to name a few, demonstration of device safety and effectiveness almost always requires clinical performance data to form the basis of product approval. In determining the safety and effectiveness of a class III device, some of the factors considered by FDA include the intended use of the device; the population for which the device is intended; device reliability; and the risk of device use compared with the likely benefit incurred by using the device. To make a determination of product safety and effectiveness, the Agency relies on *valid scientific evidence*.[3 †]

The main goal of FDA device review is to properly assess the clinical utility of the device, based on its risk and benefit profile, to determine product safety and effectiveness. The FDA has a statutory requirement to review a PMA application in a total of 180 days. As will be further discussed in this chapter, the FDA's interpretation of valid scientific evidence for medical device approval has become more rigorous for cardiovascular devices over the last decade, incorporating greater use of randomized, controlled, and even blinded studies when applicable (see Chapter 1).

*21 C.F.R., Part 814.

†21 C.F.R. § 860.7(c)(2) valid scientific evidence is defined as "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can be fairly and reasonably concluded by qualified experts that there is a reasonable assurance of the safety and effectiveness of a device under its conditions of use."

Table 4–1 Comparison of Device and Drug Development

Developmental Feature	Device	Drug
Rate of technology change	Fast	Slow
Ease of in vitro assessment	High	Low
Ability to blind treatments	Difficult	Easy
Influence of physician technique on results	High	Low
Ability to visualize performance after use	High	Low
Pivotal studies required	1	2
Population size	Smaller	Larger

Adapted from: Foy JR, Muni NI: Regulatory considerations for drug-eluting stents. In Stone GW (ed): Textbook of Coronary Stenting, in press.

Investigational Device Exemption

Clinical studies performed in the United States using devices that present a significant risk to human subjects (most class II devices and all class III devices) are performed under an approved exemption by the FDA, called an Investigational Device Exemption (IDE). FDA approval of an IDE application gives a manufacturer permission to conduct a clinical study of an investigational device (or an approved device for non-approved indications) on patients in the United States to support the device's safety and effectiveness. As per FDA regulations, the purpose of the IDE is to "encourage…the discovery and development of useful devices intended for human use, while at the same time protecting the public health and ensuring that clinical investigations are performed in a safe and ethical manner."[4 ‡] To maintain optimum freedom for scientific investigators in the pursuit of device development, the statutory time requirement for the FDA to complete its review of an IDE application is 30 calendar days. Clinical data obtained from a study under an approved IDE can then be used to support a 510(k) or PMA application, depending on the pathway necessary for marketing.

Differences in Device and Drug Regulation

There are significant differences in the regulation of devices and drugs by the FDA, largely a result of two main factors (1) differences in the characteristics and use of device and drug therapies; and (2) differences in the regulatory mandate given to the FDA by the U.S. Congress. Table 4–1 provides a comparison of key differences in device and drug development. The differences, as listed in the table, greatly affect the manner in which devices are evaluated compared with drugs, including device-related as well as population-related factors. Of major importance, because a double-blind clinical study is not possible for many cardiovascular device therapies owing to the physical characteristics of the device, the potential for patient and physician-related bias to confound study outcome is increased. For example, in the case of the REMATCH trial, in which end-stage heart failure patients were randomized to left ventricular assist device (LVAD) therapy or optimal

‡21 C.F.R. §812.1(a)

medical management arms,[4] the study could not be blinded for obvious reasons. The inability to blind clinical studies contrasts with the accepted paradigm of double-blinded, placebo-controlled trials for drug therapies.

Many device studies require a "roll-in" phase, owing to time-related improvement in outcome in the use of the device as a result of a physician learning curve. For example, many trials of new robotic surgery assist devices and intravascular embolic protection devices include roll-in phases, such that changes in physician proficiency with use of a new technology can be evaluated vis a vis their impact on clinical performance. There is no comparable learning curve phenomenon for drug administration. Additionally, recipient populations for most cardiovascular devices are proportionately smaller compared with many drug therapies (for example, circulatory assist devices for heart failure patients compared with angiotensin-converting enzyme inhibitor therapy), reducing the sample pool eligible for a clinical study and necessitating smaller device trials compared with drug trials.

Significant differences in FDA regulations affect how devices and drugs are evaluated. For drug therapies, the approval process begins with preliminary testing of a new product in animals, followed by a filing of an Investigational New Drug Application (IND). Clinical testing of an investigational drug usually proceeds in phases, unlike device evaluation. Phase I trials, testing the metabolism and safety of the new drug in a small number of healthy volunteers, is performed initially. Subsequently, phase II studies, generally dose-ranging studies to evaluate safety and efficacy in the patient population, take place, and finally larger phase III pivotal trials evaluating safety and efficacy in a larger, more heterogeneous patient population are completed. Data from these studies are submitted in a New Drug Application (NDA) to the FDA, requesting marketing approval for the investigational drug. The FDA usually requires at least two randomized, controlled, pivotal phase III trials for drug approval, compared with a single trial for device therapies. Post-approval, late stage (phase IV trials, safety registries, effectiveness trials) studies are often conducted to evaluate the effect of the product in various subpopulations and at varying doses or indications, and its long-term benefit and risk profile. The post-approval device evaluation process is discussed in a following section.

Differences in U.S. versus European Device Regulation

The concept of a single European Union (EU) system of medical device regulation is comparatively new and still evolving. In contrast to a single agency in the United States tasked with enforcing regulatory requirements for pre-market notification and pre-market approval of medical devices, the EU currently relies on a system of Notified Bodies for marketing clearance of medical devices. Conformity among the various Notified Bodies, designated and monitored by national authorities within the EU, is guided by three main directives.[5] * The Notified Bodies are responsible for carrying out regulatory inspections of medical device manufacturers and their products under each of the three directives, but the directives are not legally binding to member states. The Directives define the essential requirements that must be met by medical devices when they are placed in commercial use. In general, medical devices can be marketed only if they were subject to a risk assessment, a risk management process, and a risk and benefit analysis. Devices that have met the essential requirements specified by the Directives are then CE Marked by the Notified Body to which an application was submitted for review. The CE Mark is a formal statement of compliance with the requirements of the Directives. Of note, a key difference between U.S. and European regulatory approaches to medical devices is that the U.S. regulatory system is based on confirming that devices are safe and effective for their intended use, whereas the European system is modeled to a large extent on assuring device safety. Although device performance is a concern, the CE Mark indicates only that the manufacturer meets the conformity assessments as established in the Directives.

THE TEMPLE REPORT AND EVOLUTION OF THE DEVICE REGULATORY PROCESS

As discussed in the prior section, the FDA's evaluation of devices is significantly different compared with the evaluation of drugs. However, the device evaluation paradigm has been under a process of evolution over the last decade, incorporating many characteristics typical of drug evaluation. Much of the convergence of the device and drug evaluation processes can be attributed to the recommendations generated by an internal review of the FDA's device approval system in 1993 by the Temple Committee, chaired by Dr. Robert Temple of the FDA's Center for Drug Evaluation and Research (CDER).

The Temple Report and Its Impact on Device Regulation

In the early 1990s, there was growing concern that the FDA was hampered in its ability to properly judge the safety and effectiveness of medical devices owing to limitations in the designs of supportive clinical studies for PMA and 510(k) applications. As a result, the Commissioner of Food and Drugs, Dr. David Kessler, convened a committee primarily composed of clinical and statistical reviewers from CDER, led by Dr. Robert Temple. The Committee on Clinical Review, also known as the Temple Committee, performed reviews on selected pending and approved device applications. The Committee was then asked to make recommendations on improving the clinical review process. The Committee report, also known as the Temple Report, was presented to the public in March 1993.[6] † The Temple Report identified numerous deficiencies in the design and analysis of clinical trials performed by manufacturers for PMA and 510(k) applications.

*Active Implantable Medical Devices Directive (90/385/EEC), June 20, 1990; Medical Devices Directive (93/42/EEC), June 14, 1993; In Vitro Diagnostics Medical Devices Directive (98/79/EC), December 7, 1998. http://europa.eu.int/comm/enterprise/medical_devices/legislation_en.html

†"Final Report of the Committee for Clinical Review: Based on a Review of Selected Medical Device Applications," U. S. Food and Drug Administration, March 1993.

The following key deficiencies were identified by the Temple Committee in its review of selected applications:

- Failure to specify clear hypotheses to be tested and development of clear plans to test them
- Failure to use the most appropriate kind of control or to identify any control group at all
- Use of poorly defined historical controls
- Use of sample sizes inadequate to answer questions
- Poor specification and characterization of patients entering studies
- Poor or no assessment of the comparability of patients in treatment and historical control groups
- Failure to define study endpoints clearly and consistently
- Failure to consider and use blinded evaluation of endpoints where endpoints are subjective

The Temple Committee concluded that, as a result of the identified deficiencies in pre-market submissions submitted to the FDA for review, the FDA was seriously hindered in making appropriate determinations of substantial equivalence or safety and effectiveness for devices. The deficiencies resulted in lengthy review times owing to the multiple requests by the FDA for additional data from the manufacturer. As a result of the Temple Committee's findings and recommendations, CDRH's review and guidance practices have greatly evolved since the 1993 report. Some of the most significant changes include the use of more randomized, controlled studies; better characterization of inclusion/exclusion and success criteria; development of prospective statistical hypotheses and analysis plans; and incorporation of blinding where possible. Although there has been a convergence over the last decade toward drug-like clinical trials, the differences in device versus drug characteristics preclude a completely analogous approach for device and drug regulation. The Division of Cardiovascular Devices at CDRH strives to maximize the use of previously developed drug approaches, while also recognizing that devices are not drugs. Hence, creative approaches, such as the use of nonrandomized studies and propensity score and Bayesian statistical methodology, have become parts of the cardiovascular device clinical trial landscape in certain circumstances (see Chapter 1).[5]

Randomized versus Nonrandomized Studies

Determination of what constitutes *valid scientific evidence* depends on a variety of factors and can vary according to the type of technology and the risk posed by the device. FDA considers data from randomized, controlled clinical trials (RCTs) to be the standard of scientific evidence and encourages use of RCTs in cardiovascular device studies (see Chapter 1). However, use of an RCT study design may be especially challenging in some areas of cardiovascular device development owing to sample size issues or ethical dilemmas. Lack of clinical equipoise for cardiovascular disease management, as in the case of life-sustaining device therapies for end-stage disease, can create ethical dilemmas by mandating that patients be randomized to a study arm that may be perceived by clinicians and/or patients to provide an inferior treatment. The FDA understands that a proper assessment of device technology must balance the competing demands of maximizing scientific validity against the practical realities of performing (and effectively completing) these clinical studies.[6] For this reason, use of nonrandomized clinical studies may be acceptable in certain situations for support of a marketing application. For example, incremental design changes to an existing cardiovascular device, such as an EP ablation catheter, well-characterized with engineering and animal testing data, may be evaluated for safety and effectiveness with a single-arm clinical study in some circumstances. Use of a nonrandomized study design, however, must include the careful selection of a suitable historical control. Additionally, a detailed statistical analysis plan should be developed that accounts for differences in baseline clinical covariates and other time-related improvements in cardiovascular disease management that could bias against historical control data. Statistical methodologies, such as propensity score analysis, could be used as an attempt to increase balance in measured covariates between nonrandomized treatment arms.[7] However, the limitations of propensity score analysis, as well as other means of analysis of nonrandomized data, must be recognized.

Endpoints in Cardiovascular Device Trials

To make a determination of a device's safety and effectiveness, thorough consideration must be given to selection of the most informative and relevant endpoints for clinical trials. For most cardiovascular devices, clinical outcome parameters such as death, myocardial infarction, stroke, length of hospitalization and/or readmission, to name a few, are usually appropriate. Endpoints representing combinations of such clinical parameters, such as major adverse cardiac events (MACE), and target vessel failure (TVF), are often used, either as composite endpoints as described above or as co-primary endpoints with other parameters.

With some cardiovascular devices, successive improvements in device technology have led to decreased rates of adverse events. Improvement in patient outcome is clearly desirable, but has the effect of making comparative analysis between devices more difficult. Coronary drug-eluting stent (DES) technology is one example of this*: the two currently approved DES, the CYPHER Sirolimus Eluting Stent and the TAXUS Paclitaxel Eluting Stent, were tested against bare metal stent controls in their pivotal trials, SIRIUS and TAXUS IV, respectively,[8,9] and demonstrated a reduction in major cardiac adverse event rates.

Given the rapid adoption of DES technology as the standard of care for coronary interventions, current trials for new DES technologies have adopted non-inferiority, active control study designs, in which event rates for both treatment arms are much lower than those observed in bare metal stent trials. Assuming that successive generations of DES have even lower expected adverse event rates, it is expected that study populations much larger than those used in a DES versus placebo study will be necessary to conduct trials with adequate power

*It should be noted that coronary drug-eluting stents are officially classified by the FDA as combination drug–device products, with features of drug as well as device therapies. Based on official designation by the FDA, CDRH has served as the lead review center for DES, with CDER serving a consultative role. Hence, the clinical testing pathway for DES has followed the PMA pathway for device approval.

to discern relevant treatment differences from the noise of clinical endpoints. To allow for a practical and logistically feasible way to prevent an inflation of required sample size to preserve study power, alternative strategies to determine product effectiveness may be appropriate.

Surrogate endpoints have been suggested as alternate outcome measures for technologies such as DES. Angiographic markers of restenosis, including diameter stenosis and late lumen loss, are potential surrogate markers for clinical effectiveness endpoints. These angiographic outcome measures have the advantage of providing quantitative data for comparison, even in patients who have not developed a major clinical adverse event, and consequently have the potential for increasing the effect size of outcome measures between treatments. Other biomarkers have been proposed as surrogates for other device studies, such as myocardial infarct size and electrocardiographic ST-segment resolution for intracoronary embolic protection devices. An increase in outcome rates and/or magnitude of measured events has the benefit of reducing the required sample size for adequate power to evaluate product effectiveness. Although the use of biomarkers as surrogate endpoints has potential advantages, proper validation of the surrogate variable must be undertaken to fully characterize its predictive capabilities compared with clinical outcomes. The appropriate manner in which to characterize and validate biomarkers for use as surrogate variables in device trials remains a point of contention.[10,11]

Study Blinding in Cardiovascular Device Trials

Although the use of study blinding reinforces the integrity of the random allocation and treatment effect of patient assignment in RCT study designs, for most cardiovascular devices, designing a purely blinded RCT can be impractical and logistically impossible because of the physical characteristics and/or the mode of action of the device. However, it is very important to consider the potential for considerable investigator and/or patient bias introduced by knowledge of treatment assignment, possibly confounding clinical study outcomes and diminishing the scientific validity of a study. Study designs should, therefore, incorporate blinding to the maximum extent possible, maintaining the blind for patients, follow-up study investigators, and study staff to minimize the potential for bias and confounding, whenever logistically implementable. In addition, increasing the objectivity of study outcome parameters as much as possible, and including special analytical methods to evaluate for the potential influence of bias in study outcome are potential ways to maximize the scientific validity of study design.

As an example, the pivotal studies conducted for the CYPHER and TAXUS drug-eluting stents used double-blind study designs, given that the products visually and radiographically were similar in appearance. However, with noninferiority DES trials, in which stents with different platforms are being used, the cardiac catheterization laboratory staff is aware of treatment assignment because of the unique physical properties of each product. Hence, a single-blind approach has been recommended in which patients, the device manufacturer, and study staff, except for the cardiac catheterization laboratory staff, are all blinded to treatment assignment.

Use of Foreign Data for U.S. Product Approval

Increasingly, studies for cardiovascular devices are conducted in centers outside the United States (OUS). The FDA is allowed to consider OUS data as supportive evidence for U.S. product approval.* However, as specified in the regulation, OUS data must be demonstrated to be *applicable to the U.S. population and practice of medicine*. Unless consideration of the potential differences in patient populations and study characteristics is made before initiating OUS studies, such data might have limited applicability.

There are potential advantages to combining data from different studies, including the ability to evaluate device performance across a broader population than can be achieved by one study alone. In addition, multiple studies performed at different sites could potentially increase the generalizability of study results because of wider demographic and geographic inclusion. Furthermore, demonstration of comparable device performance across different studies can provide a more robust conclusion of product safety and efficacy.

A key consideration when assessing the applicability of OUS studies in support of product safety and effectiveness is to evaluate the generalizability of the OUS studies to the patient population in the United States. Important factors include patient-related demographic and clinical characteristics, geographic differences in medical practice, and differences in study protocol. These factors have the potential to affect cardiovascular device performance in terms of both safety and effectiveness. Planned statistical analyses could be used to evaluate the comparability of U. S. and OUS data, by testing the homogeneity of demographic and procedural covariates across centers and geographical regions as well as testing for interactions between treatment and region.

Independent Oversight of Cardiovascular Device Trials

Many cardiovascular device studies evaluate breakthrough approaches that have novel technologies and potential unforeseen risks to patients enrolled in clinical trials. To ensure adequate protection of patient safety, the FDA has increasingly recommended the use of independent Data Safety and Monitoring Boards (DSMB) (see Chapter 1). Study DSMBs should have adequate monitoring plans to adequately ensure that patients are not subjected to undue risk. In cases where cardiovascular devices are evaluated in multiple, concurrent trials, it may be appropriate to use the same DSMB to streamline safety monitoring from a "global" perspective.[12]

In the spirit of the Temple Commission report, the FDA has increasingly recommended the use of independent oversight and adjudication committees to avoid potential issues of conflict-of-interest and external bias. Interpretation of cardiovascular trial data by independent core labs, with adjudication of clinical events completed by a clinical events committee (CEC), complements the role of the study DSMB by further reinforcing study integrity and independent monitoring.

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*21 CFR § 814.15.

RISK, BENEFIT, AND THE PRODUCT LIFE CYCLE

The regulatory mandate given by Congress to the FDA was to ensure a *reasonable assurance* of a device's safety and effectiveness before allowing the device to be marketed. The requirement of reasonable assurance reflected the understanding that there was no regulatory mechanism that would guarantee *absolute* safety and effectiveness of a medical device. Implicit in the requirement for reasonable assurance was the recognition that the context of the risk and benefit profile of the illness being treated is essential to determine a device's safety and effectiveness. In other words, effective medical devices may have the capacity to do harm, and an assessment of a device's safety and effectiveness should take into account the device's risk weighed against the potential benefit in terms of clinical utility. Although the reasonable assurance mandate allows the FDA to rely on prudent risk and benefit assessments in its decision-making process, this requirement adds to the complexity of the FDA's task in determining the appropriate level of information needed before allowing a product to be marketed, given that there is no "one size fits all" approach for medical devices. Throughout a device's life cycle, risk and benefit assessments must be made by the FDA to protect and promote public health.

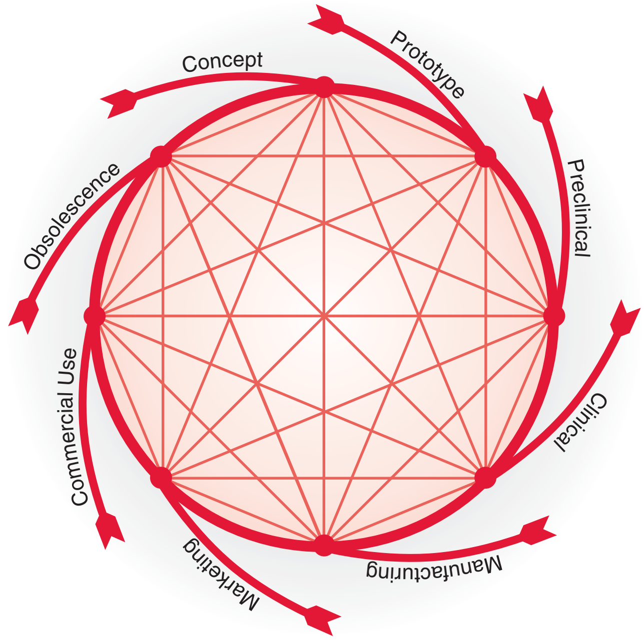

Figure 4–2 The Total Product Life Cycle. (Redrawn from the U.S. Food and Drug Administration.)

The Total Product Life Cycle Approach

All medical devices have a finite product life cycle, from the concept phase to product obsolescence (Fig. 4–2). The FDA views device development in terms of a continuum of development phases, in which product risk and benefit evaluation must take place across all stages of the product life cycle. Compared with drug therapies, the product life cycle for most cardiovascular devices is much shorter, with an average concept-to-obsolescence time between 1 and 2 years, compared with many years for an average drug. The optimal regulatory strategy must take into account the rapid product life cycle of cardiovascular devices. Novel approaches are necessary to evaluate serial iterations of existing technologies, so that a product is not confined to obsolescence after completion of a clinical trial designed to test the first generation device. Allowing manufacturers to submit supplements to already approved PMA applications is one approach to streamline the regulatory review process for incremental device changes. In addition, approaches to device regulation must view the product life cycle in its entirety, viewing the pre-clinical development, clinical testing, and marketing of a device not as divided phases but as a continuing spectrum of development.

Striking an Appropriate Pre-approval/ Post-approval Balance

One of the most complex tasks faced by the FDA for class III devices is finding the proper balance between assessing product safety and effectiveness versus making promising therapies readily available to the public. To achieve an appropriate balance, the FDA must consider several competing factors across all stages of a product development life cycle. For example, initiation of a clinical study requires the adequate determination of safety based on pre-clinical laboratory, engineering, and animal testing. Approval of class III (and some class II) devices for marketing subsequently requires an adequate determination of safety and effectiveness based on data generated from clinical testing. Risk and benefit evaluation continues in the post-approval setting, by means of device safety evaluation when used in "real world" clinical practice, including important cohorts of patients often not tested in initial testing for product approval. The optimal pre-approval/post-approval balance for collecting device safety and effectiveness information must weigh the risks of allowing an incompletely tested product to be marketed to the public against the risks of delaying a potentially lifesaving or life-enhancing product from being made available to patients.

The Cardiologist's Role in Assuring Device Safety and Performance

The primary goal of the FDA in evaluating cardiovascular devices is to ensure that the devices are safe and effective—in other words, that the products confer maximum benefit on patients without imposing unreasonable risks. FDA uses a variety of regulatory tools, applied before the marketing of a product as well as after it is in widespread use, to assist in assessing product safety and effectiveness. However, making sure that devices are safe and effective is a task for which the FDA's efforts can go only so far. Clinicians have a vital role to play in completing this process: by knowing the clinical indications of the devices they use, by understanding and documenting the potential adverse effects they may encounter, and by informing patients about benefits and risks.

Specifically, it is important for all physicians to review a product's instructions for use (IFU) statement, usually an insert included within the device packaging, regarding the populations tested in supportive clinical studies, and to be

thoroughly familiar with the approved indications for use as well as the instructions for using the product. It is equally important that clinicians and support staff at health care facilities be familiar with the FDA's MDR system for product-related adverse events, and that they report such events expeditiously.* Without the reports of device-related adverse events submitted by physicians and health care facilities, the FDA would be impeded in identifying a potential safety problem with a device.

ENSURING THE SAFETY OF MARKETED DEVICES

Although pre-clinical and clinical testing of cardiovascular devices provides invaluable information on short-term safety and effectiveness in a select population, performance of a device in populations not specifically tested in clinical trials ("real world" use) and over the long-term are not addressed by such testing. Furthermore, pre-clinical and clinical studies performed for device approval might not detect certain low-occurrence events but would detect catastrophic adverse events that would render an investigational product unacceptable for general use. Such low-occurrence events might be detected only in large-sample study populations and over longer follow-up periods, making it necessary to gather further information in actual clinical use. Hence, there is a need for continued device evaluation after a product is allowed on the market.[13]

Post-market Safety Assessment Tools

The increased speed of technology turnover, shorter product life cycles, and the prohibitive cost of conducting full-scale, randomized clinical trials for medical devices contributes to the importance of post-marketing surveillance studies to evaluate long-term device performance. Surveillance of medical devices post-approval provides a system in which risks and benefits can be assessed in a larger population and over a longer period of follow-up than would be achievable in the pre-marketing phase. Unanticipated risks secondary to product manufacturing changes, device modifications, or human factors (such as changes in operator technique) usually cannot be adequately tested in pre-clinical and clinical testing models.

Effective post-approval identification of device risks relies on the active collaboration of device manufacturers, regulatory bodies, physicians, and health care facilities to detect and report device-related injuries and other adverse events. Given the differences in regulatory mechanisms in the post-market oversight of medical devices compared with pre-market regulations, post-market device evaluation is largely dependent on information provided voluntarily by device manufacturers and health care providers.[14]

There are several different methods to collect post-approval clinical information for devices, each with differing levels of scientific validity. Table 4–2 provides examples of different post-approval device study methodologies, from the highest level of scientific rigor to purely qualitative, adjunct forms of data collection. Under current Medical Device Reporting (MDR) regulations, the FDA requires that device manufacturers report all device-related deaths and serious injuries to the Agency. One difficulty the FDA faces in assessing adverse event information obtained by this route is that underreporting of adverse event information, especially by clinicians and end-users, is widespread. Furthermore, given the absence of denominator information (the total number of devices actually used), assessment of adverse event rates is not reliable via this mechanism. Accurate determination of adverse event rates requires a controlled study with defined follow-up periods.

Table 4–2 Examples of Post-approval Data Collection Methods

- Randomized, blinded controlled clinical trial
- Randomized, nonblinded clinical trial
- Comparative and noncomparative cohort clinical study
- Case-control study
- Registry study
- Survey
- Active surveillance
- Passive Surveillance via Medical Device Reporting (MDR) system, Medical Device Safety Network (MedSun), and International Vigilance

Examples ranked in order of level of "scientific rigor," starting from the most scientifically valid method of data collection to purely descriptive and potentially more biased forms of obtaining data.

Pre-market and Post-approval Integration

To enhance integration of the pre- and post-approval stages of device risk and benefit evaluation, a novel mechanism using continued access, "peri-approval" registry studies has been used for two drug-eluting stents under development.[10 †] To expedite the acquisition of traditional post-marketing data, the FDA has allowed the initiation of post-approval registry studies during the pre-approval stage in these circumstances, permitting a manufacturer to continue collecting data under the auspices of the original clinical study, but with expanded clinical access, for post-approval device evaluation. Such an approach has the benefit of allowing for quicker initiation of post-approval studies as well as providing additional acute safety data to support marketing approval itself for the device. Approval of the pre- and post-marketing study plans simultaneously allows for continuous enrollment without gaps

*Adverse events can be reported online at http:www.fda.gov/cdrh/mdr.

†"CYPHER sirolimus-eluting coronary stent on RAPTOR over-the-wire delivery system or RAPTORRAIL rapid exchange delivery system—P020026." Rockville, Md.: Food and Drug Administration, April 24, 2003. (Accessed July 25, 2005, at http://www.fda.gov/cdrh/pdf2/p020026.html.) and "TAXUS Express 2 paclitaxel-eluting coronary stent system(monorail and over-the-wire)—P030025." Rockville, Md.: Food and Drug Administration, March 4, 2004. (Accessed July 25, 2005, at http://www.fda.gov/cdrh/pdf3/p030025.html.)

during FDA review and approval decision-making, and accommodates IRB approval during the initial clinical phase of the study, thereby minimizing potential delays in commencing the peri-approval registries. The benefit of the peri-approval approach is that both the FDA and a device manufacturer can, in a timely fashion, assess patient safety in a more representative, "real-world," use of the device.

Off-Label Use of Cardiovascular Devices

One of the most important aspects of the device approval process is the development of a meaningful and accurate product label, which includes the indications for which the product is approved, instructions for use, and patient-related information. The FDA works closely with the device manufacturer to create the product label. The label also includes details regarding the clinical studies performed in support of the product's approval, and the specific population tested in clinical studies.

Physicians may want to use a device in a manner different from the labeled indication (i.e., an "off-label" use) because the beneficial effects seen in clinical trials may transfer to relatively untested patient subgroups. A legally marketed device may be used as the physician deems appropriate to benefit an individual patient as part of the *practice of medicine*. However, both the physician using an off-label device and the patient on whom the device is used should understand that the off-label use may not have been tested sufficiently to establish its risk and benefit profile, and that generalization of available trial results to broader patient populations may not be appropriate.

Although off-label use by a physician in the routine practice of medicine is not within the FDA's regulatory purview, the Agency is concerned that off-label device use diminishes the incentive for a manufacturer to study or seek FDA approval for the indication for which the product is being used off label. Additionally, not having adequate data to evaluate the safety and effectiveness of devices in important patient subsets limits the ability of a clinician to decide whether or not a specific product is appropriate for their patient, and greatly hinders the process of appropriately informing patients of the risks and benefits of such therapy.

If physicians use a device for an indication not in the approved labeling, they have the responsibility to be well informed about the product, base the product's use on firm scientific rationale and on sound medical evidence, and maintain records of the product's use and effectiveness. Specific language introduced by the FDA Modernization Act of 1997 addressed "practice of medicine,"* stating that *nothing in this act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner–patient relationship.* However, the Act did make clear that promotion of medical devices did fall under the Agency's purview, and therefore, promotional activity for medical devices must be consistent with the device's approved labeling.

*21 U.S.C. 396 § 906, see also Food and Drug Modernization Act of 1997 § 214.

CONCLUSION

As part of the responsibility to protect the public health, the FDA faces many challenges in the evaluation of new cardiovascular devices. Given the rapid advancement of cardiovascular device technology, the FDA must determine how to best achieve its mandate with the resources at its disposal. It is clear that an active collaboration of industry, the clinical community, and regulatory agencies is essential to maximize efficiency and best expedite the advancement of new technologies across all stages of the product development life cycle. Along with the anticipated changes in the technological and clinical landscapes of cardiovascular medicine, the FDA's technology assessment programs will continue to evolve to maximize regulatory efficiency and to provide the most appropriate means of evaluating risk and benefit of medical devices. At the same time they must ensure that beneficial therapies are made available to patients in a timely manner.

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Ischemic Heart Disease

Chapter 5

Pharmacologic Options for Treatment of Ischemic Disease

Jonathan Abrams, John Schroeder, William H. Frishman, and Jane Freedman

CHAPTER CONTENTS

THE ORGANIC NITRATES

Organic nitrates, therapeutic agents that have been used to treat angina for more than 125 years, are known as putative exogenous nitric oxide (NO) donors.[1] They are rapidly converted to NO, which activates guanylate cyclase in smooth muscle cells and platelets. This results in the production of cyclic guanosine monophosphate (cGMP), with subsequent vascular relaxation and platelet antiaggregatory effects (Fig. 5–1). Normally, in response to a number of physiological stimuli, particularly shear stress, intact vascular endothelium releases endogenous NO, which causes vasodilation. It has been speculated that NO donors (e.g., nitrates) may circumvent the requirement for normal endothelial function and promote vasorelaxation even when the endothelium is damaged or dysfunctional (i.e., the organic nitrates may represent an exogenous source of NO). This hypothesis has not been proved, and there are no clinical data supporting the concept that organic nitrates can effectively replace endogenous NO, with a concomitant improvement in vascular function of subjects with endothelial dysfunction. Furthermore, considerable data suggest that nitrates can actually induce endothelial cell dysfunction.[2]

Mechanisms of Action

Pharmacodynamics

The major action of the nitrates is to produce *vasodilatation*, which occurs most prominently in the venous capacitance vessels, the large coronary arteries, and, to a much lesser extent, in the peripheral arterioles and microvasculature.[3,4] Through a reduction of preload and afterload, oxygen uptake of the heart is decreased by about 20% to 40%.[3] The fall in myocardial oxygen demand reflects reductions in venous return and both left and right ventricular volumes, along with a modest fall in arterial pressure, although these benefits may be to some extent offset by a reflex increase in the heart rate.[5]

Nitrates have direct effects on the coronary circulation because they dilate large coronary epicardial arteries and arterioles that are more than 100 μm in diameter. Nitrates do not effectively dilate the smaller arterioles or resistance vessels, possibly because the enzymes responsible for converting organic nitrate to NO are relatively inactive or absent in the smaller coronary arterioles and microcirculation.[5] By dilating large coronary arteries, nitrates may favorably redistribute blood flow to collateral channels and blood flow from epicardial to endocardial regions, as well as attenuate exercise-induced coronary arterial constriction and spontaneous coronary spasm.[4] In addition, these agents may prevent or reverse constriction of sites of coronary stenoses. An important clinical distinction is that agents such as dipyridamole and other vasodilators, including sodium nitroprusside (SNP) that act directly on small arterioles and the microcirculation may induce a *coronary steal* effect by diverting nutrient blood flow from ischemic regions of the myocardium.[6]

Vascular Signaling Systems

The production and release of endogenous NO (see Fig. 5–1) are recognized as having an extraordinarily important physiological role that extends beyond the cardiovascular system.[7] Nitrate biotransformation to NO may occur near the plasma membrane of vascular smooth muscle cells; a certain amount of extracellular transformation of organic nitrate to NO also takes place.[8,9] The activity of the enzyme glutathione-*S*-transferase as well as the presence of thiol groups may

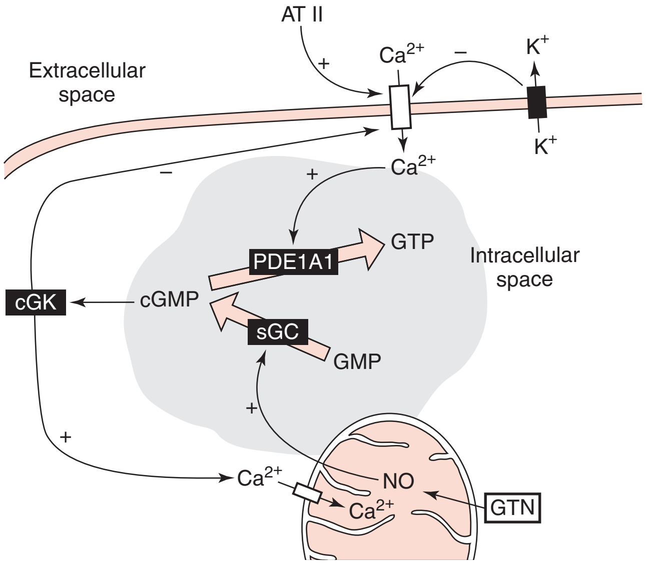


Figure 5–1 **Mechanisms of nitrate action**. GTN is metabolized to NO, which stimulates the synthesis of cGMP. In turn, cGMP reduces cytoplasmic Ca^{2+} by inhibiting inflow and stimulating mitochondrial uptake, causing relaxation of smooth muscle cells. The role of Ca^{2+}-activated K^+ currents is also being investigated. By inducing hyperpolarization of the cellular membrane, they might contribute to the limitation of Ca^{2+} entry in smooth muscle cells and, in endothelial cells, they might inhibit O_2^- production. By promoting Ca^{2+} uptake, ATII can increase cytoplasmic Ca^{2+} and induce the Ca^{2+}-dependent PDE1A1. This may lead to reduced cGMP and cGK activity, providing an elegant explanation for both nitrate tolerance and increased sensitivity to ATII. There is evidence supporting a redox sensitivity of all enzymes involved in these processes. PDE1A1 indicates phosphodiesterase 1A1; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; AT II, angiotensin II. (Redrawn from Gori T, Parker JD: Nitrate tolerance: A unifying hypothesis. Circulation 2002; 106:2510.) (Note: GTN = NTG = nitroglycerin. The abbreviations GTN and NTG are used interchangeably in the text and figures in this chapter.)

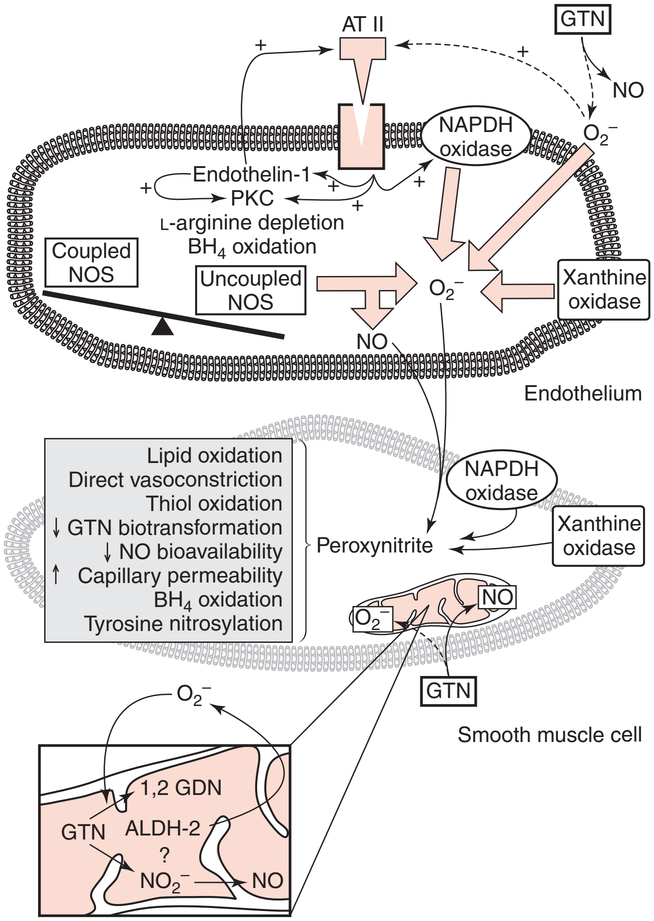


Figure 5–2 **Proposed mechanisms of nitrate tolerance, emphasizing oxidative stress**. Diagram depicting the proposed pathways for the development of nitrate tolerance. Both endothelial and smooth muscle cells are involved in these processes. Superoxide anion is produced by membrane oxidases and, possibly, during nitroglycerin (glyceryl trinitrate; GTN) biotransformation (*dashed arrow*). Increased angiotensin II (AT II) production and responsiveness and increased oxidative stress may result in uncoupling of nitric oxide synthase (NOS) and further production of reactive oxygen species and peroxynitrite. In turn, these oxidant-free radicals may cause many of the abnormalities observed in nitrate tolerance. Isoprostane formation and increased capillary permeability might be responsible for plasma volume expansion, and tyrosine nitrosylation and thiol group oxidation might be responsible for inactivation of multiple enzymes—including those involved in the biotransformation of nitroglycerin. Tetrahydrobiopterin (BH_4) oxidation may cause NOS uncoupling. PKC, protein kinase C; O_2^-, superoxide anion; GDN, glyceryl dinitrate; NO_2^-, nitrite. (Redrawn from Parker JD: Nitrate tolerance, oxidative stress, and mitochondrial function: Another worrisome chapter on the effects of organic nitrates. J Clin Invest 2004;113:352.)

be required, but this remains controversial. Not all data are consistent with this hypothesis, and other enzyme systems—including an esterase and a microsomal cytochrome P450—have been reported to produce NO even in the absence of sulfhydryl groups.[10] Sulfhydryl-dependent metabolism has been thought to be important to the development of nitrate tolerance,[11] although recent work has de-emphasized this older concept. Especially promising is the suggestion that biotransformation of nitroglycerin (NTG) occurs predominantly in mitochondria through a novel reduction of mtALDH (mitochondrial aldehyde dehydrogenase or ALDH-2) (Fig. 5–2).[1,9,12-15] Furthermore, Chen and colleagues believe that "attenuated biotransformation of NTG by mitochondrial ALDH underlies the induction of nitrate tolerance"[9,12] (see later). The importance of mitochondrial ALDH in modulating the development of nitrate tolerance, however, is controversial and not accepted by some authorities in the field (J. Horowitz, personal communication, 2005). Arguments against a central role for mitochondrial ALDH in producing tolerance include

1. ALDH can be inhibited by NTG under conditions in which almost no tolerance is induced.
2. ALDH inhibitors produce the same effects in tolerant and nontolerant vessels.
3. Chinese subjects who lack ALDH2 respond either normally or nearly normally to NTG at both vascular and platelet levels.

Nitrates are more active in venous tissue than in arteries, and vascular uptake of nitrate is more avid in the veins than in the arteries.[16] The rate of formation of cGMP is surprisingly greater in arteries than in veins.[17]

Effects on Platelets

A modest inhibitory effect of nitrates on platelet aggregation has been demonstrated in vitro, ex vivo, in normal subjects, and in patients with angina or recent acute myocardial infarction (MI). Low concentrations of nitroglycerin (NTG) can partially reverse adenosine diphosphate (ADP)-induced platelet aggregation.[18] The clinical significance of this effect is unknown, but antiplatelet activity after nitrate administration may play a beneficial role, particularly in unstable angina.[4,19]

Intracellular Actions of Nitric Oxide

NO stimulation of guanylate cyclase results in cGMP production, in turn activating a cGMP-dependent protein kinase.[10] This kinase decreases cytosolic calcium levels in vascular smooth muscle cells—the "ultimate step" in vascular contraction. The mechanism for the fall in calcium levels is not yet well understood but might involve (1) increased uptake of Ca^{2+} into the sarcoplasmic reticulum (after phosphorylation of phospholamban); (2) decreased release of Ca^{2+} from the sarcoplasmic reticulum after a fall in inositol-1,4,5-triphosphate; or (3) inhibited contraction after decreased phosphorylation of the controlling enzyme in vascular smooth muscle contraction—namely, myosin light-chain kinase. cGMP also has direct effects on monovalent cation transport. Furthermore, NO has effects on potassium channels independent of cGMP. Thus, the pathways involved in nitrate-induced vasodilatation remain uncertain, although those shown in Figures 5–1 and 5–2 represent one current view of nitrate biotransformation. Not all investigators are in agreement with this scheme.[11]

Direct Effects on Myocardium

The direct action of NO on cardiac muscle produces a negative inotropic effect,[20] which could contribute to the anti-ischemic protection of nitrates. The potential messenger for myocardial responsiveness to NO may also be cGMP, which by lowering cell calcium levels could theoretically protect against calcium-mediated ischemic damage and arrhythmias.

Summary of Hemodynamic Actions of Nitrates

The predominant clinically relevant effect of the nitrates is a combination of preload reduction, modest reduction in afterload, and dilatation of large epicardial coronary arteries (including nonobstructed sites of vasoconstriction or at the coronary stenosis) (Table 5–1).[3,4] Other mechanisms of action, such as those on platelets, prostaglandins, and cardiac myocytes, are not yet definitely established as being important in reducing myocardial ischemia.

Pharmacokinetic Properties of Nitrates

The pharmacokinetic properties of the individual organic nitrates vary greatly (Table 5–2).

Nitroglycerin. Plasma NTG levels, difficult to measure, transiently increase in the case of sublingual NTG, and result in sustained blood levels with transdermal NTG patches. With continuous NTG delivery systems, NTG levels are maintained relatively constant for a 24-hour period, although there is intra-individual and inter-individual variability. Transdermal NTG patches should be removed after 12 to 14 hours of use each day.

Isosorbide dinitrate and isosorbide mononitrate. Hepatic first-pass extraction converts circulating isosorbide dinitrate (ISDN) to isosorbide-5-mononitrate (5-ISMN), the active component, and, to a lesser extent, to 2-mononitrate. All three of these compounds reach high concentrations in the plasma. Approximately 50% to 60% of the parent compound ISDN is converted to 5-ISMN.

5-ISMN is completely absorbed with nearly 100% bioavailability. Both standard and controlled-release formulations have been extensively studied. Whenever steady-state blood levels of the organic nitrates are maintained for a significant period of time, nitrate tolerance may develop. Long-term dosing schedules designed to avoid nitrate tolerance are established for 5-ISMN (two 20-mg doses of the standard preparation are administered 7 to 8 hours apart), as well as for ISDN (maximum of two or three doses per day). Controlled-release ISDN or 5-ISMN preparations are administered as a single dose once daily. Standard doses and preparations are shown in Table 5–2.

Indications for Nitrates

Nitrates are used for the treatment of a wide variety of anginal syndromes, including acute effort angina (sublingual, buccal, or oral spray NTG); stable angina prophylaxis (oral, topical, or buccal); unstable angina (intravenous, topical, or oral); acute MI (intravenous); and congestive heart failure (intravenous, topical, or oral).

Nitrate Therapy for Congestive Heart Failure

The combination of long-acting nitrates and hydralazine was one of the first regimens to show that vasodilator therapy could favorably influence outcome in chronic heart failure.[21] Several studies have documented favorable acute hemodynamic benefits with organic nitrates, which include lowering of left ventricular filling pressure (pulmonary wedge pressure of LVEDP) and lowered pulmonary artery pressure, accompanied by only small changes in blood pressure.[22-24] Higher nitrate doses than those used in angina pectoris are usually necessary in heart failure, such as 60 to 90 mg of oral ISDN, 2 to 3 inches of NTG ointment, or 0.6 to 1.0 mg/hr transdermal NTG. Intravenous NTG or ISDN may be especially useful in critically ill patients in florid congestive heart failure. A study from Israel demonstrated superior efficacy of high-dose intravenous ISDN compared with high-dose furosemide plus low-dose ISDN in subjects with severe pulmonary edema.[25] The African-American Heart Failure Trial (A-HeFT)[26] may stimulate increased use of an ISDN-hydralazine combination in heart failure (see later). It is likely that nitrate therapy in heart failure is underused by many physicians. A survey of >300 heart failure specialists confirms use of nitrates in up to 80% to 90% of such patients, with greater use in sicker subjects.[27] Coadministration of hydralazine was reported in at least 25% of patients.

Table 5–1 Beneficial Effects of Nitrates in Angina Pectoris: Potential Mechanisms of Action

Peripheral or Systemic Actions	Result
Venous dilation (systemic and pulmonary veins)	Smaller right and left heart volumes (preload and afterload) Lower right and left heart filling pressures (preload) Altered LV pressure-volume relationship
Arterial dilation	Reduced arterial reflectance wave Decreased systolic blood pressure Increased arterial compliance Decreased aortic impedance Increased efficiency of LV ejection Decreased LV afterload
Arteriolar dilation (high doses)	Decreased systemic vascular resistance Decreased afterload
Central or coronary action Coronary artery (epicardial) vasodilation Prevention/reversal of coronary artery vasoconstriction and spasm Coronary stenosis dilation (eccentric lesions) Enhanced collateral caliber and flow Prevention of distal coronary vessel and/or collateral constriction Preserved coronary vasodilator response in the presence of endothelial dysfunction Dilation of small (resistance) vessels with large doses	All actions: increased global and/or regional coronary blood flow, especially during ischemia
Endothelial function Nitrates converted to nitric oxide within vascular smooth muscle cell, which diffuses into lumen	Vasodilation and antiplatelet action in the absence of normal endothelial function
Antiplatelet actions* Decreased platelet aggregation and adhesion	Potential antithrombotic benefit in unstable angina and acute myocardial infarction

*Controversial.
LV, left ventricular.
From Abrams J: Nitrates. Cardiol Clin Ann Drug Ther 1997;1:25–40.

Nitrate Tolerance

The phenomenon of nitrate tolerance, once under dispute and ignored by many clinicians, is now established beyond reasonable doubt. The precise mechanism or mechanisms involved remain incompletely resolved (see Fig. 5–2). Nitrate tolerance occurs clinically whenever nitrate blood levels are sustained for many hours without a nitrate-free interval or major fluctuations in nitrate levels. Of interest, organic nitrate plasma levels are elevated in the presence of tolerance. Tolerance has been documented during nitrate treatment of congestive heart failure as well as in stable angina pectoris. Although there is relatively little direct evidence for tolerance when intravenous nitrates are administered for unstable angina or acute MI, increasing dosage is often required to control chest pain; it is likely that some diminution of nitrate action occurs during continuous intravenous administration of NTG or ISDN in unstable angina or acute MI.

Proposed Mechanisms of Tolerance—Old and New

In vitro, vascular tolerance is accompanied by reduced metabolic conversion of nitrates to the pharmacologically active product, NO.[11] This concept is supported by in vivo data in which the amount of exhaled NO decreases as nitrate tolerance develops; with the direct NO donor sodium nitroprusside, tolerance does not develop, nor is there any decrease in exhaled NO.[28] There are a wide variety of hypotheses regarding the pathogenesis of tolerance.[15,29] Many experts believe that there are multiple contributing mechanisms, and no overriding theory is accepted by all.

The **Sulfhydryl Hypothesis** suggests that the process of NO formation from organic nitrates depletes intracellular sulfhydryl groups.[11] When blood vessels are studied in vitro, there is substantial evidence for the sulfhydryl theory; nevertheless, the validity of the sulfhydryl or thiol hypothesis has long been questioned. In isolated vessel experiments, extremely high concentrations of NTG are often used and tolerance may be induced within 1 hour. However, in clinical situations, nanomolar nitrate concentrations are therapeutically effective, whereas the exposure time for nitrate tolerance to develop is at least several hours. Sulfhydryl donors such as acetylcysteine or methionine (indirect sulfhydryl donor) could theoretically counteract tolerance by providing sulfhydryl

Table 5–2 Nitrate Formulations: Dosing Recommendations and Pharmacokinetics*

	Usual Dose (mg)	Onset of Action (min)	Effective Duration of Action
Sublingual NTG	0.3–0.6	2–5	20–30 min
Sublingual ISDN	2.5–10.0	5–20	45–120 min
Buccal NTG	1–3 p.m. or t.i.d.	2–5	30–300 min†
Oral ISDN	10–60 b.i.d. to t.i.d.	15–45	2–6 hr
Oral ISDN-SR	80–120 daily	60–90	10–14 hr
Oral ISMN	20 b.i.d.‡	30–60	3–6 hr
Oral ISMN-SR	60–120 daily	60–90	10–14 hr
NTG ointment	0.5–2.0 inch t.i.d.	15–60	3–8 hr
NTG patch	0.4–0.8 mg/hr§	30–60	8–12 hr

*Higher doses are often required in heart failure.
†Effect persists while tablet intact in buccal cavity.
‡Two daily doses at least 6 hr apart (e.g., 8 o'clock, 3 o'clock).
§Patch should be removed daily for 10-12 hr.
ISDN, isosorbide dinitrate; ISMN, isosorbide mononitrate; NTG, glyceryl trinitrate (nitroglycerin); SR, sustained release.
From Abrams J: Nitrates, Cardiol Clin: Ann Drug Ther 1997;1:25-40.

(-SH) groups within the vascular cells or by forming extracellular nitroso-thiols (RSNO) (see Fig. 5–1), which could enter the vascular cell to directly stimulate guanylate cyclase.[11] In human volunteers, acetylcysteine may provide some protection against nitrate tolerance in veins but not in medium-sized arteries.[28] However, the overall evidence regarding the use of *N*-acetylcysteine to prevent or treat nitrate tolerance remains confusing (see reviews by Boesgaard and coworkers,[30] Fung and Bauer,[11] and Horowitz[15]). In any case, the practical problem of providing exogenous thiols with coadministered nitrates precludes such an approach—except in experimental situations. Although the thiol depletion theory is historically important and well established experimentally, it is no longer considered by many experts to be the primary explanation of nitrate tolerance.[15,29,31,32] However, a new finding does support a rationale for thiols in biotransformation of nitrates to NO (see mitochondrial aldehyde hydrogenase discussion later) (see Fig. 5–2).[9,12-15]

Neurohumoral hypothesis. This construct proposes that nitrate-induced venous dilatation leads to preload reduction and reflex activation of the renin-angiotensin and adrenergic systems that result in compensatory arteriolar vasoconstriction, which may reduce renal perfusion and function.[29,33-37] In congestive heart failure, a prolonged NTG infusion increases plasma catecholamines, endothelin, and renin activity; whereas the levels of vasodilatory atrial natriuretic peptide decrease.[33] Consequently, there also may be impaired salt and water regulation with fluid retention; hematocrit falls during prolonged NTG patch application and body weight increases. Concurrent angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blocker (ARB) administration may lessen nitrate tolerance in congestive heart failure; at the least, the combination of the two drugs may be clinically effective. However, the benefits of combined ACE inhibitor and ARB nitrate administration have not been consistent; significant improvement with combination therapy has been seen in some, but not all, reports.[29,34-36]

Oxidant stress-vasoconstriction hypothesis. The work of Munzel, Bassenge, Harrison, and their colleagues has suggested an important mechanism for nitrate tolerance.[15,31,32,37-39] These investigators conclusively demonstrated that vascular exposure to organic nitrates results in endothelial cell production of oxygen-free radical species, which increase vascular smooth muscle cell sensitivity to angiotensin II, endothelin, and catecholamines. Experimental damage to, or removal of, the endothelium results in less attenuation of nitrate action.[15,38] These observations link the endothelium as a contributor to attenuated nitrate effects. This hypothesis provides a potential therapeutic role for antioxidants in the reduction of oxidant stress as well as the decreased likelihood for development and maintenance of tolerance. A number of studies have demonstrated a possible role for vitamins C and E, as well as other antioxidants, such as hydralazine, to reduce or prevent tolerance.[39-42] However, Fung has proposed a complex explanation for nitrate tolerance that does not support oxidative stress as the primary mechanism of nitrate tolerance (see below).[43]

Mitochondrial aldehyde hydrogenase (ALDH-2) hypothesis. In 2002, Chen, Zhang, and Stamler proposed that the enzyme mALDH or ALDH-2 is primarily responsible for biotransformation and denitrification of NTG, catalyzing the conversion of NTG to 1,2-glyceryl dinitrate within the mitochondria.[12-15] High concentrations of NTG, as well as inhibitors of ALDH-2, decreased vascular relaxation induced by organic nitrates (i.e., promoted the development of NTG tolerance). The authors suggest that "...build-up of NTG and/or NO byproducts in mitochondria may result in mitochondrial damage and uncoupling of respiration.[13] Furthermore, oxidative stress and reactive oxygen species attenuated NTG biotransformation." Thus, ALDH-2 inhibition is postulated to be a major cause of nitrate tolerance. Subsequently, Munzel and coworkers linked nitrate tolerance with inhibition of ALDH-2 and impairment of NTG metabolism, endothelial dysfunction, and increased mitochondrial production of ROS.[13] These investigators believe "mitochondrial dysfunction plays a key role in evolution of nitrate tolerance." Parker and Gori further evaluate these phenomena in several detailed commentaries.[14,31,32] In 2005, Chen and associates published evidence that the bioconversion by mALDH of clinically relevant concentrations of NTG results in activation of guanylate cyclase, production of cGMP, and vasodilatation.[9] Furthermore, it was shown that inactivation of mALDH occurred with continued exposure to NTG and was an important mechanism for the development of nitrate tolerance.[9] (See earlier comments about controversy regarding mALDH and nitrate tolerance).

Thionitrate oxidation. H.L. Fung, a long-standing contributor to our knowledge of nitrate pharmacotherapeutics, suggests that multiple thiols are important in the bioactivation of nitrates and are involved in the development of nitrate tolerance.[8] He disputes that the mitochondrial aldehyde dehydrogenase hypothesis is the sole contributor to nitrate biotransformation and subsequent nitrate tolerance (personal communication).

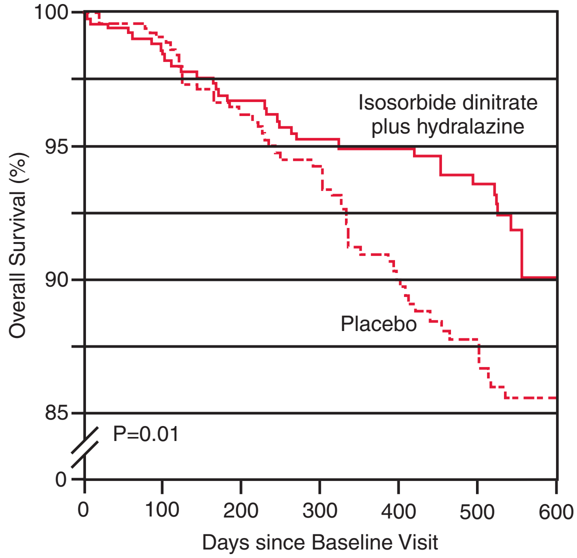
Autonomic nervous system hypothesis. New research suggests an interaction of organic nitrates with the autonomic nervous system (ANS) at both peripheral and central sites. For

instance, NO synthesis in the brain stem inhibits medullary areas that modulate sympathetic outflow; this action is lost in the presence of nitrate tolerance—possibly related to abnormal central nervous system nitric oxide synthase (NOS) activity.[44] "A tolerance-dependent loss of a sympathoinhibitory mechanism might blunt the vasodilatory responses to NO donors in resistance vessels, thus contributing to nitrate tolerance."[45] Increases in brain O_2, as well as angiotensin II, may modulate these alterations. Chronic nitrate therapy may result in increased sympathetic outflow and decreased parasympathetic tone. In a pig model, chronic nitrate administration decreased the number of NO-producing neurons in the brain stem with a loss of inhibitory effects of NO on sympathetic excitability.[44] These phenomena could contribute to nitrate tolerance.

L-Arginine hypothesis. L-arginine, the immediate precursor of NO, is depleted in the presence of nitrate tolerance; this contributes to oxidative stress and uncoupling of NOS, resulting in increased L-arginine requirements and relative L-arginine depletion. There is a related reduction in stores of tetrahydrobiopterin (BH_4), a situation that further contributes to impaired NO availability and uncoupling of NOS.[15,31,32] Replenishment of BH_4 by folic acid increases NOS but may not reverse tolerance. Peroxynitrate can oxidize BH_4, increasing NOS but also oxidative anions. Folate replacement increases BH_4 stores and can prevent or reverse nitrate tolerance, independent of the antioxidant effects of folic acid.[46] These phenomena may be characterized as injury to the arginine transport system caused by exogenous nitrates. Considerable data suggest that folate or L-arginine supplementation results in sustained NOS function and the prevention or amelioration of nitrate tolerance.[42,46-49]

The nitrate-hydralazine relationship. Experimentally, concurrent hydralazine administration during nitrate therapy prevents hemodynamic tolerance in heart failure.[22-24,50] Hydralazine also helps to maintain renal blood flow when it is coadministered with ISDN.[22] It is now recognized that hydralazine may act in part as an antioxidant, reducing oxidant stress and its adverse effects on tolerance.[24,50] Thus, the protective role of hydralazine may be to quench oxidative stress in the presence of organic nitrates. A number of studies have combined isosorbide dinitrate (ISDN) and hydralazine (H) and demonstrated positive results without tolerance in congestive heart failure (CHF) subjects. In the first Vasodilator Heart Failure Trial (V-HeFT I), this combination was effective in reducing mortality compared with placebo and the α-blocker prazosin.[21] That study was the first to demonstrate a decrease in mortality in any CHF drug trial. In retrospective analyses of both V-HeFT-I and V-HeFT-II, the combination of ISDN and hydralazine was noted to be more effective in blacks than in whites.[51] Other data suggest differences in endothelial vasodilator responses between black and white subjects.[52]

The African-American Heart Failure Trial (A-HeFT), completed in 2004, was designed in part because of the positive data with an ISDN-H combination.[26] The A-HeFT rationale capitalized on the concept of increased NO availability by provision of both ISDN and hydralazine to African-American heart failure patients. It has been suggested that blacks have decreased endothelial vasomotor responses, decreased nitric oxide (NO) responsiveness, and a less active renin angiotensin system than whites.[51,52] The A-HeFT study enrolled 1005 black subjects with class III or IV heart failure or left ventricular enlargement, who were followed for a mean of 10 months.[26] Mortality was reduced by 43% in the active treatment cohort when compared with placebo subjects, along with a comparable composite endpoint reduction (first rehospitalization and quality of life measurements). The differences between the drug combination and placebo were robust (Fig. 5–3).



No. at Risk

Placebo	532	466	401	340	285	232	24
Isosorbide dinitrate plus hydralazine	518	463	407	359	313	251	13

Figure 5–3 **Kaplan-Meier estimates of overall survival.** The A-HeFT investigators reported that a fixed dose of isosorbide dinitrate plus hydralazine increased survival when added to standard therapy in black patients with heart failure. (Redrawn from Taylor AL, Ziesche S, Yancy C, et al., for the African-American Heart Failure Trial Investigators: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2052.)

Of particular interest is the possibility that hydralazine, known to be a free radical scavenger, may have prolonged the physiological activity of ISDN, allowing for protracted hemodynamic benefits with less or no nitrate tolerance during the course of the trial. The authors suggest that hydralazine provided "protection against the degradation of nitric oxide induced by oxidative stress,"[26] although specific direct evidence supporting this hypothesis is not available. Considerable experimental data confirm that decreases in NO availability and endothelial vasomotor dysfunction are common in models of heart failure, with a host of adverse consequences related to impaired cardiac muscle function. Furthermore, the concept that hydralazine prolongs the duration of nitrate efficacy, attenuating or even preventing nitrate tolerance, is critical to the design of A-HeFT. The strongly positive A-HeFT results, although not definitive, appear to support the "hydralazine is an antioxidant" hypothesis, as suggested by Munzel and colleagues in 1996.[50]

In June 2005, the United States Food and Drug Administration approved an ISDN-hydralazine combination pill (BiDil) for use in the United States. It is likely that this combination will subsequently be tested in a variety of clinical conditions. If, as remains unproven as of this writing, a free radical scavenger such as hydralazine can truly sustain nitrate action without adverse sequelae, nitrates will again be in the forefront of cardiovascular therapy.

Several outstanding reviews of nitrate bioactivation and nitrate tolerance are recommended to the interested reader.[14,15,31,32,46] It is clear that the nitrate tolerance story remains incomplete and unsolved. The thiol and oxidative stress theories are compelling. Interactions between organic nitrates, oxidative stress, and thiols of various origins, appear to be pivotal, but we still have far to go to understand and unravel these complex phenomena.

Can Nitrates Be Harmful?

It has long been assumed that therapy with organic nitrates is beneficial, or at least neutral, in the presence of nitrate tolerance. Coronary artery vasoconstriction following acetylcholine administration during coronary angiography after NTG transdermal patch removal has been documented.[53] Rebound symptoms of nocturnal angina have been noted in several studies during the patch-off period with intermittent NTG patches therapy in subjects with angina.[54] A retrospective data analysis from Japan[55] and a post hoc analysis of two randomized clinical trials[56] suggest that long-term nitrate therapy in patients with coronary disease may be associated with adverse clinical outcomes. These provocative data, if confirmed, could explain in part why nitrates were not shown to reduce morbidity and mortality rates in the two large post-MI clinical trials, ISIS-4 and GISSI-4. As discussed, data from nitrate tolerance studies confirm increased oxidative stress, decreased biotransformation of NTG, decreased eNOS activity, and endothelial dysfunction in the presence of nitrate administration. These phenomena suggest that nitrate tolerance may not be neutral or benign.

Prevention of Tolerance

The use of eccentric dosing with short-acting oral nitrates (ISMN, ISDN) (e.g., two doses per day administered 7 to 8 hours apart) is the simplest and most reliable method to avoid tolerance.[11,29,57-59] Many studies in patients with effort angina show that tolerance can be avoided or minimized with an interval dosing approach. A single daily dose of a long-acting oral nitrate (ISDN, 5-ISMN) is also effective in preventing tolerance, presumably because this allows for rising and falling plasma drug levels. Nitroglycerin patch administration requires an intermittent dosing strategy of 12 to 14 hours on and 10 to 24 hours off each day. Even when nitrate tolerance is established, sublingual nitrates retain their therapeutic effect. Dose escalation with nitrates may be useful in avoiding or overcoming nitrate tolerance in patients with congestive heart failure and coronary syndromes.[60]

Nitrate Cross-tolerance

Tolerance to long-acting nitrates may also result in cross-tolerance to short-acting nitrates, and vice versa, as shown for forearm capacitance vessels, coronary artery diameter, and exercise tolerance performance during intravenous NTG therapy.[5]

Tolerance versus Resistance

High intravenous NTG doses (in excess of 200 μg/min) or very large doses of ISDN occasionally have no hemodynamic effect, even when administered in the absence of earlier nitrate therapy. This phenomenon has been called *nitrate resistance* and has been well documented in congestive heart failure.[15,60,61] Intense renin-angiotensin activation and accelerated tolerance induction may contribute to nitrate resistance, which is generally seen only in severe biventricular heart failure.

Side Effects of Nitrates

Headaches are the most common adverse effect of nitrate therapy; they often lead to loss of patient acceptance of the prescribed nitrates. A decrease in headaches over time is common and may reflect in part subjective adaptation, arterial tolerance, or both.

Hypotension (e.g., systolic blood pressure of less than 100 mm Hg systolic) occurs in about 10% of patients receiving low-dose intravenous NTG and can be reversed by discontinuing the infusion or reducing the rate. With oral nitrates, symptomatic hypotension seldom occurs without other therapies, such as β-adrenergic antagonists or dihydropyridine calcium blockers. Reduction of the dose of either drug or a change of agent should be considered in such cases. Many individuals experience dizziness, presyncope, or even syncope on initial exposure to sublingual NTG.

Other occasional adverse effects include hypoxemia in patients with chronic lung disease due to increased ventilation-perfusion mismatch. Prolonged high-dose intravenous NTG therapy has rarely caused methemoglobinemia with cyanosis.

Nitrates and Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors are used to treat sexual dysfunction in men; they include sildenafil, tadalafil, and valdenafil.[62] These agents improve penile erectile function by increasing smooth muscle relaxation which results in engorgement of the corpus cavernosum, venous compression, and sustained penile rigidity. The mechanism of action—prolonged PDE-5 inhibition—allows for greater and longer cGMP action, thus enhancing male sexual function. The three drugs available have demonstrated a high level of improvement in men with erectile dysfunction (ED) of many causes.

The risk of an adverse pharmacologic interaction of PD5 agents in the presence of organic nitrates is the development of major hypotension that results from increased NO availability, coupled with decreased cGMP degradation. Thus, nitrates, including sublingual and transdermal nitroglycerin, are contraindicated during exposure to the PDE-5 inhibitors. The duration of time from ingestion of a PDE-5 inhibitor during which nitrates are precluded is variable, and depends on the drug used. For the short-acting agents—sildenafil and valdenafil—the "no nitrate" time frame is 24 hours, but for the longer acting tadalafil, this period is up to 48 hours, during which time concomitant use of a nitrate and the PDE-5 inhibitor is clearly contraindicated.[60]

Combination Therapy for Anginal Syndromes

Although abundant clinical experience supports the practice of combining nitrates with β-blockers and/or CCBs in the therapy of anginal syndromes, there is no evidence that the addition of nitrates to the use of other antianginal agents decreases morbidity or mortality rates.[58] Nitrate-dosing regimens used in most older studies have often been subsequently shown to cause tolerance.

The combination of β-blockade and nitrates is standard in the therapy of angina. β-blockers decrease heart rate and arterial blood pressure and may increase left ventricular cavity size; nitrates act primarily by reducing preload and, to a lesser degree, afterload, and they often result in tachycardia and a smaller heart. There do not appear to be pharmacokinetic interactions between these two classes of drugs.

CCBs and nitrates are also often combined, yet there is relatively little clinical trial evidence of an increased antianginal effect. When a nitrate is used, the addition of a nondihydropyridine (non-DHP) (e.g., verapamil, diltiazem) is preferable to the nifedipine-like DHPs because of the significant afterload reduction induced by the short-acting DHPs. The hemodynamic actions of verapamil and diltiazem resemble those of β-blockers, with a negative inotropic effect and a modest slowing of heart rate, whereas the short-acting DHPs may reflexively increase heart rate. The recommended combinations for chronic stable angina are a nitrate plus a β-blocker, a nitrate plus a rate-slowing CCB, or a β-blocker plus a DHP CCB.[58,59]

Triple therapy with nitrates, β-blockers, and CCBs is frequently used in subjects with continuing angina. Nonetheless, such an approach carries the risk of excess hypotension, as well as potential adverse interactions between a β-blocker and a rate-slowing CCB (e.g., additive negative inotropic effects, additive sinoatrial, atrioventricular nodal inhibition with verapamil or diltiazem). Furthermore, no clinical trial data are available to support the efficacy of a three-drug regimen.

Direct Nitric Oxide Donors: Sodium Nitroprusside

SNP is the prototype of a direct NO donor, releasing NO into the vascular smooth muscle cell without requiring enzymatic conversion (see Fig. 5–1). Thus, SNP vasodilates all vessels, both venous and arterial, and the microcirculation. Perhaps because this agent is a direct NO donor, tolerance has not been documented with its use. SNP vasodilates the small coronary arterioles (less than 100 mm in diameter), which could induce a coronary steal phenomenon, in the setting of coronary atherosclerosis. In an important study, Mann and coworkers[6] showed that when SNP was administered to patients with coronary artery disease, regional myocardial blood flow decreased significantly. In contrast, after sublingual NTG administration, regional flow increased. For that reason, SNP is not the drug of choice when blood pressure reduction is required in the presence of active myocardial ischemia. Nonetheless, the drug is appropriate in severe or acute congestive heart failure requiring intravenous afterload and preload reduction in the absence of ongoing myocardial ischemia.

SNP is converted to cyanomethemoglobin and free cyanide in red blood cells; the free cyanide is further converted to thiocyanate in the liver and cleared by the kidneys with a half-life of 7 days. Thus, cyanide may accumulate with prolonged high doses of SNP and produce lactic acidosis. Inactivation of cyanide by the liver may be limited by the availability of thiol groups, and administration of thiosulfate can protect against SNP toxicity.[63]

SNP remains useful for the acute management of hypertensive emergencies and severe congestive heart failure. It is administered only intravenously, the solution must be protected from light, and tissue extravasation should be avoided. Blood pressure monitoring with either an indwelling arterial catheter or automatic noninvasive system is required because of the potential for a rapid fall in blood pressure.

CALCIUM CHANNEL BLOCKERS

CCBs are agents that inhibit several specific calcium-dependent functions in the cardiovascular system. By decreasing vascular smooth muscle contraction and tone, they produce peripheral and coronary vasodilatation. The non-DHPs have a negative inotropic effect, which is an undesired action if it becomes excessive. Certain CCBs (e.g., verapamil, diltiazem) inhibit calcium-dependent SA and AV nodal conduction. The CCBs are approved for use in hypertension, angina pectoris, and acute supraventricular tachycardias. In the United States, the most commonly used available CCBs are diltiazem, verapamil, nifedipine, amlodipine, and felodipine. Bepridil, isradipine, and nicardipine are available but are used relatively infrequently; nimodipine is usually used only for subarachnoid hemorrhage or ruptured cerebral aneurysm.

Fundamental Mechanisms of Calcium Channel Blockers

Calcium Channel as Site of Action

CCBs interfere with the entry of Ca^{2+} into cells through voltage-dependent L- and T-type calcium channels.[64] The major cardiovascular sites of action are (1) vascular smooth muscle cells, (2) cardiac myocytes, and (3) SA and AV nodal cells. By binding to specific sites, known as subunits, in the proteins of the calcium channel, these agents are able to diminish the degree to which the calcium channel pores open in response to voltage depolarization (Fig. 5–4).

Molecular Structure. The calcium channel consists of four high-molecular-weight subunits, named α1, α2, β, and γ. Of these, it is the α1 subunit that contains the calcium channel pores and the binding sites for CCBs. The subunits have a complex structure with four major domains (see Fig. 5–4), each with six transmembrane units.[65] The calcium channel pores exist between the fifth and sixth units. The voltage sensor is located near the fourth transmembrane unit of each domain.

There are two important regulatory aspects of calcium channel blockade. First, when cyclic adenosine monophosphate (cAMP) activates protein kinase A to phosphorylate the calcium channel, there are a number of phosphorylation sites on the COOH-terminal portion of each of the α1 subunits. Such phosphorylation allows the channel to persist in a more open state. Second, the β subunit binds to the cytoplasmic link between the domains I and II of the γ1 subunit and thereby enhances calcium channel opening.[64]

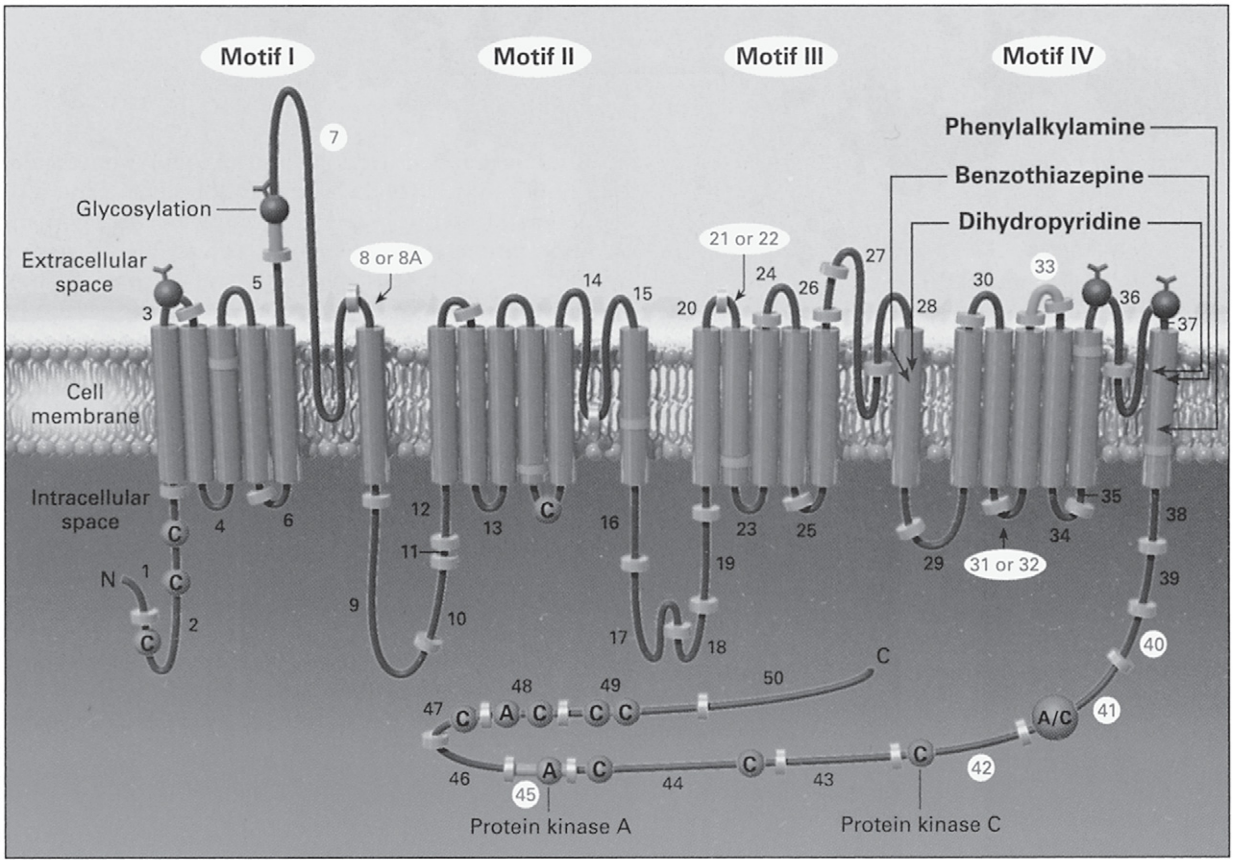


Figure 5–4 (*See also Color Plate 5–4*). **Proposed arrangement of the polypeptide chain of the channel-forming α_{12} subunit of the L-type calcium channel in humans.** There are four repetitive motifs (I, II, III, and IV), and each consists of six putative transmembrane segments. Both the N terminal and the C terminal point to the cytoplasm. Rings separate the segments encoded by numbered exons. The transmembrane segments encoded by alternative exons 8 or 8A, 21, or 22, and 31 or 32 are shown. Sequences encoded by invariant exons 7, 33, and 45, which are subject to constitutive splicing, are also shown. Exons 40, 41, and 42 are subject to alternative splicing. Putative sites of glycosylation and of phosphorylation involving protein kinase C (C) and protein kinase A (A) are shown, as are the discrete binding areas of the three types of calcium antagonists—phenylalkylamine (verapamil-like), benzothiazepine (diltiazem-like), and dihydropyridine (nifedipine-like). (From Abernethy DR, Schwartz JB: Calcium-antagonist drugs. N Engl J Med 1999;341:1448.)

Drug-Binding Sites. There are at least three binding sites for these drugs, commonly known as the V, or phenylalkylamine; N, or DHP; and D, or benzothiazepine, binding sites (identified by the prototype agents verapamil, nifedipine, and diltiazem, respectively). The N-binding site is also termed the DHP site, to which all DHPs are thought to bind. Each of the different agents binds to specified sites on various domains, and none binds to all of the pores in all the domains. Thus, calcium channel blockade can never be complete.

Calcium Channels: L and T Types

The most important property of the CCBs is to selectively inhibit the inward flow of charge-bearing Ca^{2+} when the calcium channel becomes permeable, or "open." There are at least two types of calcium channels relevant to the treatment of cardiovascular disorders: the L and T types. The major calcium channel related to pharmacologic antagonism, the voltage-gated L-type (long-acting, slowly activating) channel, is blocked by all available CCBs. The function of the L-type channel is to allow entry of sufficient Ca^{2+} for initiation of contraction by calcium-induced intracellular calcium release from the sarcoplasmic reticulum.

The T-type (transient) channel appears at more negative potentials than the L type and probably plays an important role in the initial depolarization of SA and AV nodal tissue. The L-type calcium channel is found in vascular smooth muscle, nonvascular smooth muscle in many tissues, and a number of noncontractile tissues. Blockade of the L-type channel is responsible for the pharmacologic actions of the available CCBs.

Pharmacologic Properties of Calcium Channel Blockers

Pharmacodynamic Effects

Despite their structural diversity and binding differences, CCBs display many common important pharmacologic actions. However, there are significant differences between the sites of action of the DHPs and non-DHPs (Table 5–3).

Table 5–3 Vasodilator Potency, and Inotropic, Chronotropic, and Dromotropic Effects of Calcium Channel Blockers on the Heart

	Amlodipine	Diltiazem	Nifedipine	Verapamil
Heart rate	↑/0	↓	↓	↓
Sinoatrial node conduction	0	↓↓	0	↓
Atrioventricular node conduction	0	↓	0	↓
Myocardial contractility	↓/0	↓	↓/0	↓↓
Neurohormonal activation	↑/0	↑	↑	↑
Vascular dilatation	↑↑	↑	↑↑	↑
Coronary flow	↑	↑	↑	↑

↓ = decrease; 0 = no change; ↑ = increase.
Adapted from Abernethy DR: Pharmacologic and pharmacokinetic profile of mibefradil, a T- and L-type calcium channel antagonist. Am J Cardiol 1997;80:4C-11C, with permission from Excerpta Medica Inc.

Major Cardiovascular Actions of Calcium Channel Blockers

1. *Vasodilatation*: This effect is more marked in arterial and arteriolar vessels than on veins and includes the coronary vasculature; veins do not appreciably dilate with CCBs.
2. *Negative chronotropic and dromotropic effects* on the SA and AV nodal conducting tissue (non-DHP agents only)
3. *Negative inotropic effect* on myocardial cells; in the case of DHPs, this effect may be offset by reflex adrenergic stimulation after peripheral vasodilatation.

Classification of Calcium Channel Blockers

The differing pharmacodynamic effects of various CCBs accounts for the classification of the CCBs. All the DHPs bind to the same sites on the α1 subunit and exert a greater Ca^{2+} inhibitory effect on vascular smooth muscle than on the myocardium, which explains their common property of vascular selectivity. Thus, their major hemodynamic and therapeutic effect is peripheral and coronary vasodilatation.

Nifedipine is the prototypical DHP. The fast-acting capsular form produces rapid vasodilatation, alleviates hypertension, and terminates attacks of coronary spasm. However, the brisk peripheral vasodilatation produced by this formulation may result in significant hypotension and reflex adrenergic activation, often causing tachycardia and stimulation of the sympathetic and renin-angiotensin systems. The introduction of truly long-acting DHP compounds, such as amlodipine or sustained-release formulations of nifedipine, felodipine, or isradipine, has resulted in substantially fewer symptoms owing to vasodilatory side effects. It is a commonly held belief that the short-acting DHPs, particularly nifedipine, account for the majority of presumed negative or adverse clinical results in many older trials.[64,66] The second-generation DHPs are distinguished by a longer half-life, as in the case of amlodipine, or by a greater vascular selectivity.

The non-DHPs verapamil and diltiazem, although each binding to different sites on the α1 subunit, have many properties in common. Both act on nodal (SA and AV) tissue and are therapeutically effective in supraventricular tachycardias. Both decrease the sinus discharge rate. These drugs inhibit myocardial contractility more than the DHPs (i.e., are less vascular selective). Both verapamil and diltiazem have greater effects on the AV node than on the SA node; the explanation for this may relate to frequency dependence. Thus, there is better access to the binding sites when the calcium channel pore is open. During supraventricular tachycardia, the calcium channel of the AV node opens more frequently, so the CCB binds more avidly and, hence, more specifically inhibits the AV node to interrupt the reentry circuit.

Regarding side effects, because non-DHPs are less active on vascular smooth muscle, they produce fewer vasodilatory adverse reactions than the DHPs. Sinus tachycardia is uncommon, in part because of the inhibitory effects on the SA node. High-degree AV block is a risk with preexisting AV nodal disease or during cotherapy with other AV node-depressant drugs, such as β-blockers. Non-DHPs have a more marked depressive effect on ventricular function than DHPs. Constipation occurs as a side effect with verapamil but seldom with diltiazem; the latter may cause peripheral edema.

Vascular Selectivity

The cellular mechanism of vascular smooth muscle contraction differs from that of the myocardium. Although smooth muscle contraction is ultimately calcium dependent, it is the myosin light-chain kinase that is activated by calcium-calmodulin. In the case of the human myocardium, Godfraind and associates[67] proposed that the ratios of vasodilatation to negative inotropy for the prototype CCBs were 10:1 for nifedipine, 1:1 for diltiazem, and 1:1 for verapamil. Other DHP compounds have even greater vascular selectivity, up to 1000:1. In terms of clinical use, these observations provide the basis for considering a clinical division of the CCBs into two groups: the DHPs (i.e., nifedipine and its analogs) and the non-DHPs (e.g., verapamil, diltiazem, and their derivatives).

Noncardiovascular Effects

Although highly active on vascular smooth muscle, CCBs have little or no effect on other smooth muscle throughout the body, such as that of the bronchi, gut, or genitourinary tract. These agents may relax uterine smooth muscle and have been used in preterm contractions. It is generally recommended that they be stopped before delivery. This probably reflects variations between tissues in either the structure or function of their calcium channels. Also crucial to the therapeutic applicability of CCBs is the fact that skeletal muscle does not respond to conventional CCBs. As a result, skeletal muscle weakness is not a side effect of CCB. In skeletal muscle,

Table 5–4 Selected Characteristics of Trials of Calcium Channel Blockers

Study	Agents Used	No. of Patients Enrolled	Patient Characteristics
ALLHAT	Amlodipine vs. chlorthalidone vs. lisinopril	33,357	Hypertension and one risk factor for coronary artery disease
INVEST	Verapamil slow-release ± trandolapril ± hydrochlorothiazide vs. atenolol ± hydrochlorothiazide ± trandolapril	22,576	Hypertension and coronary artery disease
CONVINCE	Extended-release verapamil vs. atenolol or hydrochlorothiazide	16,602	Hypertension and one risk factor for coronary artery disease
NORDIL	Diltiazem vs. diuretics + β-blockers	10,881	Hypertension
STOP-2	Felodipine or isradipine vs. conventional antihypertensive agents	6614	Hypertension
INSIGHT	Nifedipine gastrointestinal therapeutic system vs. hydrochlorothiazide + amiloride	6321	Hypertension and one risk factor for coronary artery disease
VHAS	Verapamil vs. chlorthalidone	1414	Hypertension
MIDAS	Isradipine vs. hydrochlorothiazide	883	Hypertension
ABCD	Nisoldipine vs. enalapril	470	Hypertension and diabetes mellitus
NICS-EH	Nicardipine vs. trichlormethiazide	429	Hypertension and age >60 years
FACET	Amlodipine vs. fosinopril	380	Hypertension and diabetes mellitus
CASTEL	Nifedipine vs. clonidine or atenolol + chlorthalidone	351	Hypertension and age >65 years

ABCD: Appropriate Blood Pressure Control in Diabetes; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CASTEL: Cardiovascular Study in the Elderly; CONVINCE: Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; FACET: Fosinopril versus Amlodipine Cardiovascular Events Trial; INSIGHT: International Nifedipine Gastrointestinal Therapeutic System study—Intervention as a Goal in Hypertension Treatment; INVEST: International Verapamil Slow-Release/Trandolapril Study; MIDAS: Multicenter Isradipine Diuretic Atherosclerosis Study; NICS-EH: National Intervention Cooperative Study in Elderly Hypertensives; NORDIL: Nordic Diltiazem; STOP: Swedish Trial in Old Patients with Hypertension; VHAS: Verapamil in Hypertension and Atherosclerosis Study.
Adapted from Eisenberg MJ, Brox A, Bestauwrosan: Calcium channel blockers: An update. Am J Med 2004;116:35-43.

depolarization-activated calcium release from the sarcoplasmic reticulum is the principal source of the myoplasmic calcium rise. Thus, only the myocardium, and not skeletal muscle, responds to calcium entry through the voltage-dependent calcium channels, and the myocardium, but not skeletal muscle, has its rise in contractile calcium inhibited by CCBs.

Pharmacokinetics

From the point of view of drug interactions, all of the CCBs are metabolized in the liver by an enzyme system that is inhibited by cimetidine, azole antifungals, and hepatic dysfunction and increased in activity by phenytoin and phenobarbital. (See Appendix 1 for dosage information and drug interactions.)

Major Indications for Calcium Channel Blockers

Systemic Hypertension

The various CCBs act on peripheral arterioles. They are effective antihypertensive agents in all ethnic and age groups. All DHPs decrease peripheral vascular resistance and appear to have an additional ill-understood diuretic effect. Verapamil and diltiazem are less powerful vasodilators; some believe that their negative inotropic effect may contribute to their antihypertensive mechanism. Table 5–4 lists some major hypertension trials in which a CCB was used.

Angina Pectoris

Although the antianginal mechanisms of the different types of CCBs differ somewhat, these drugs share some properties: (1) coronary vasodilatation, especially in relation to exercise-induced coronary constriction, and (2) afterload reduction due to decreased blood pressure. In the case of verapamil and diltiazem, it is possible that slowing of the sinus node, with a decrease in nonmaximal exercise heart rate, and the negative inotropic effect, may contribute to decreased myocardial work.

As coronary dilators, the CCBs have a site of action on the coronary tree different from that of the nitrates. The CCBs act more specifically on the smaller coronary resistance vessels, where the tone is higher and the calcium inhibitory effect is more marked. CCBs are particularly effective in those types of angina caused by or exacerbated by coronary spasm or constriction, such as Prinzmetal angina or cold-induced angina. An overview of a large number of angina drug trials concluded that the CCBs have a very similar clinical efficacy to β-blockers.[68]

Supraventricular Tachycardia

Through their inhibitory effect on the AV node, verapamil and diltiazem interrupt the reentry circuit in supraventricular

tachycardias and are useful in terminating those arrhythmias. They are also effective in slowing the ventricular response in atrial fibrillation and may be used in chronic atrial fibrillation; the DHPs are ineffective for these arrhythmias because of minimal effects on the SA and AV node.

Postinfarct Protection

Verapamil is licensed in Scandinavian countries for postinfarct protection in patients in whom β-blockers are contraindicated. In the Danish Verapamil Infarction Trials DAVIT-1 and DAVIT-2, a modest protective benefit against death and cardiac ischemic events in post-MI subjects was documented in subjects without a history of heart failure.[69] Diltiazem has been shown to be beneficial in post-MI subjects with relatively normal LV function and no heart failure.[70] A short-term (2-week) study in non–Q-wave MI patients with high-dose diltiazem reduced the rates of recurrent ischemia and infarction.[70]

Specific Calcium Channel Blockers

Verapamil

After peripheral vasodilatation induced by verapamil, the cardiac output and LV ejection fraction do not increase as much as they do with the DHPs, probably owing to the negative inotropic effect and depression of contractility of verapamil.

Pharmacokinetics

The elimination half-life of standard verapamil tablets is usually 3 to 7 hours, but it increases significantly during long-term administration, as well as in patients with liver or renal insufficiency. In significant hepatic dysfunction, the dose of verapamil should be decreased by 50% to 75%. In significant renal dysfunction, such as a creatinine clearance of less than 30 mL/min, the dose should be reduced by 50%. Bioavailability is only 10% to 20% (high first-pass liver metabolism). The parent compound and the active hepatic metabolite norverapamil are excreted 75% by the kidneys and 25% by the gastrointestinal tract. Verapamil is 87% to 93% protein bound.

Dose

Oral Preparations. The usual dosage of the standard preparation is 80 to 120 mg t.i.d.. During long-term oral dosing, less frequent daily doses are needed (norverapamil metabolites). Slow-release preparations (240 to 480 mg daily) are administered once or twice daily.

Intravenous Use. For supraventricular reentry tachycardias, a bolus of 5 to 10 mg (0.1 to 0.15 mg/kg) can be administered over 2 minutes and repeated 15 to 20 minutes later if needed. After successful administration, the dose may be stopped or continued at 0.005 mg/kg/min for about 30 to 60 minutes, decreasing thereafter. When used for control of the ventricular rate in atrial fibrillation, verapamil may be administered at 0.005 mg/kg/min, increasing as needed, or as an intravenous bolus of 5 mg followed by a second bolus of 10 mg if needed. In the presence of myocardial disease or interacting drugs, a very low dosage (0.0001 mg/kg/min) may be infused and titrated upward against the ventricular response. However, safer AV slowing agents are available for patients with impaired LV systolic function (digoxin, adenosine).

Side Effects

Side effects include headaches, facial flushing, dizziness, and ankle edema—all lower in frequency than with the DHPs. Constipation occurs in up to one third of patients who receive verapamil. The negative inotropic effect of verapamil may precipitate or exacerbate congestive heart failure. When intravenous verapamil is used, the risk of hypotension is increased if the patient is receiving β-blockers or other vasodilators or has depressed cardiac function.

Contraindications

Sick sinus syndrome and preexisting AV nodal disease are relative contraindications to intravenous and oral verapamil. The effective use of oral verapamil preparations in these conditions may require a pacemaker. In the Wolff-Parkinson-White syndrome with atrial fibrillation, intravenous verapamil may promote antegrade conduction of impulses down the bypass tract, with a risk of very rapid atrial fibrillation and even ventricular fibrillation. In a wide QRS complex ventricular tachycardia, verapamil is contraindicated because the combined negative inotropic and peripheral vasodilatory effects can be fatal; furthermore, verapamil is unlikely to terminate a ventricular arrhythmia. Verapamil should not be used when there is moderate or severe LV dysfunction or severe hypotension.

Pregnancy. Category C (use only if potential benefit justifies the potential risk to fetus); no well-controlled trials are available.

Diltiazem

Diltiazem is used for the same spectrum of cardiovascular disease as verapamil: hypertension, angina pectoris, prevention of AV nodal reentry, tachycardias, and rate control in acute and chronic atrial fibrillation. The side effect profile is similar except that constipation is much less common.

Pharmacokinetics

More than 90% of oral diltiazem is absorbed, with approximately 45% bioavailability (first-pass hepatic metabolism). The onset of action is within 15 to 30 minutes; peak effects occur at 1 to 2 hours. The elimination half-life is 4 to 7 hours. Protein binding is 80% to 90%. Diltiazem is acetylated in the liver to the active metabolite desacetyl diltiazem (40% of the activity of the parent compound), which accumulates during long-term therapy. Only 35% of diltiazem is excreted by the kidneys, and 65% is excreted by the gastrointestinal tract.

Dose

The standard oral dose of short-acting diltiazem is 120 to 360 mg daily, in three or four divided daily doses. The slow-release preparations are administered once or twice daily. Generic diltiazem is available. Intravenous diltiazem (approved for arrhythmias) is administered as 0.25 mg/kg over 2 minutes with electrocardiographic and blood pressure monitoring; if the response is inadequate, the dose is then repeated as 0.35 mg/kg in 15 to 20 minutes. Acute loading therapy may be followed by an infusion of 5 to 15 mg/hr.

Side Effects

Side effects are few and limited to headaches, dizziness, and ankle edema in 6% to 10% of patients. The extended or slow-release preparations appear to have a side effect profile similar to that of placebo. Sinus bradycardia and first-degree AV nodal block (or higher) may be produced by diltiazem. It is important to avoid or reduce dosing in subjects with SA or AV nodal disease. In heart failure with significant LV dysfunction (e.g., ejection fraction of less than 35%), this drug can be hazardous. Exfoliative dermatitis and skin rash occur occasionally. The side effects of intravenous diltiazem resemble those of intravenous verapamil.

Contraindications

Contraindications are similar to those of verapamil: preexisting depression of the SA or AV node, hypotension, low ejection fraction, heart failure, and atrial fibrillation associated with the Wolff-Parkinson-White syndrome. LV failure ejection fraction of less than 40% after MI is a clear contraindication.[68]

Pregnancy. Category C (use only if potential benefit justifies the potential risk to fetus); no well-controlled trials are available.

Dihydropyridines

The major therapeutic action of the DHPs is arterial and arteriolar dilatation, which is responsible for their efficacy in hypertension and angina pectoris, as well as Prinzmetal or variant angina and Raynaud's phenomenon. Direct negative inotropic effects of the DHP drugs are minimal. Amlodipine is the CCB of choice in patients with severely depressed LV function because it does not decrease LV contractility at standard doses. There is no clinically significant evidence of the effect of DHP on either the SA or the AV node; these agents are not effective in supraventricular arrhythmias. They may be more readily combined with β-blockers in hypertension or angina pectoris than the rate-slowing CCBs, with less concern about depression of the SA and AV nodes.

First-Generation Dihydropyridines

Oral nifedipine is the prototypical dihydropyridine. It is rapidly absorbed with peak blood levels in 20 to 45 minutes. and a duration of action of 4 to 8 hours. Because of this short half-life and difficulty controlling the degree of blood pressure lowering, it is rarely used in its short-acting form. Slow-release forms are currently available and are preferred by some physicians. The dose for the slow-release form is 30 to 90 mg once a day.

Contraindications and Cautions

The short-acting forms are generally contraindicated.

Side Effects

Because DHPs have no SA or AV effects, reflex tachycardia may occur if excessive blood pressure lowering occurs. Headache can occur with any of the CCBs, but they occur more frequently with the first generation dihydropyridines.

Pregnancy. Category C (use only if potential benefit justifies the potential risk to fetus); no well-controlled trials are available.

Second-Generation Calcium Channel Blockers

Theoretically, the more vascular selective DHPs, such as felodipine, isradipine, amlodipine, and nicardipine, should be safer than nifedipine in the management of angina or hypertension—particularly when there is impairment of LV function. These drugs may produce adverse effects in patients with congestive heart failure, although felodipine and amlodipine appear to be quite safe in patients with depressed LV function.[71,72] In fact, amlodipine has been shown to have no adverse effect (and no benefit) compared with placebo in the PRAISE and PRAISE-2 heart failure trials. These compounds are the DHPs of choice in subjects with decreased LV function or a history of heart failure.

Although amlodipine is no more vascular selective than nifedipine, it has unusual pharmacokinetics, including slow onset and offset of binding to the calcium channel site and a prolonged elimination half-life.[73] The doses, pharmacokinetics, side effects, and interactions of these agents are shown in Appendix 1. Based on these pharmacokinetic-characteristics and new extensive experience with this agent in both angina and antihypertensive studies, amlodipine has become the dihydropyridine of choice by most physicians in the Western Hemisphere.

Drug Interactions of Calcium Channel Blockers

β-Blockers. Verapamil and diltiazem contribute to SA or AV nodal, as well as myocardial, depression or may interact via hepatic mechanisms with those β-blockers metabolized by the liver, such as propranolol and metoprolol. Although these drugs have been successfully combined with β-blockade in the therapy of angina or hypertension, clinicians should monitor patients for possible serious adverse effects when a rate-slowing CCB is combined with a β-blocker.

Digoxin. Verapamil increases blood digoxin levels by decreasing the renal excretion of digoxin. Enhancement of AV nodal block can be serious and even fatal when intravenous verapamil is administered to patients with digitalis intoxication.

Diltiazem. In general, drug interactions with diltiazem are similar to those of verapamil. Diltiazem has a slight or negligible effect on blood digoxin levels. Although diltiazem may be cautiously combined with β-blockade, the combination appears to be no more effective in some studies than high-dose diltiazem itself. Cimetidine may increase diltiazem bioavailability, resulting in a 50% to 60% increase in plasma diltiazem levels.

Dihydropyridines. The combination of DHPs with β-blockers is safer than that with non-DHP CCBs. When there is LV depression, the added negative inotropic effects of a β-blocker and DHP may precipitate overt heart failure, but this is unusual; amlodipine or felodipine is the CCB of choice in such individuals.

Calcium Channel Blockers: The "Safety" Controversy

Beginning in 1995, a question about the safety of all calcium channel blockers was raised when a retrospective analysis of

the short-acting form of nifedipine appeared to increase heart attacks in acute coronary syndrome patients, but the data were grouped with all CCBs. As prospective trials did not confirm these fears and physicians gained experience with the slow release non-dihydropyridines and long-acting dihydropyridines such as amlodipine, this issue gradually died. In fact, several antihypertensive trials have established the safety and benefit of these agents.[64,66]

Two completed hypertension trials with dihydropyridines and amlodipine have finally established the safety of these agents. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was a study of 33,357 patients aged >55 years with hypertension and at least one other common heart disease risk factor. The patients were randomized to one of four antihypertensive regimens: chlorthalidone, a diuretic, an α-blocker, amlodipine, the calcium channel blocker, and lisinopril, an ACE inhibitor.[74] Details of the study design and inclusion and exclusion criteria have been published. A primary outcome of combined fatal CHD and nonfatal myocardial infarction occurred in 2956 participants with no difference between the treatment groups. All-cause mortality also did not differ between the treatment groups.

A second trial entitled The Valsartan Antihypertensive Long-term Use Evaluating (VALUE) trial was designed specifically to test the hypothesis that the angiotensin receptor blocker valsartan would be superior to the dihydropyridine calcium channel blocker amlodipine for the same blood pressure control. The investigators proposed that valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high risk for a cardiovascular event. A total of 15,245 patients over the age of 50 years participated until 1450 events had accumulated and were followed a mean of 4.2 years.[75]

Blood pressure was reduced by both treatments, however, the amlodipine-based therapies were more effective, particularly early in the study, achieving a 4.0/2.1 mm Hg lower pressure in the amlodipine compared with the valsartan group at 1 month and 1.5/1.3 mm Hg at 1 year. Most importantly, there was no evidence of harm in the patient population but actually a nonstatistically significant slightly lower overall event rate occurred in the amlodipine group: 810 patients in the valsartan group (10.6%, 25.5 per 1000 patient years) and 789 in the amlodipine group (24.7 per 1000 patient years).

In addition, of the secondary outcomes, myocardial infarction was significantly ($P = 0.02$) more frequent in the valsartan group compared with the amlodipine group (Fig. 5–5). It has been hypothesized by the authors that the lower blood pressures in the calcium channel group may explain the lack of superiority of the angiotensin receptor blocker but it seems highly unlikely that it could also explain the statistically significantly

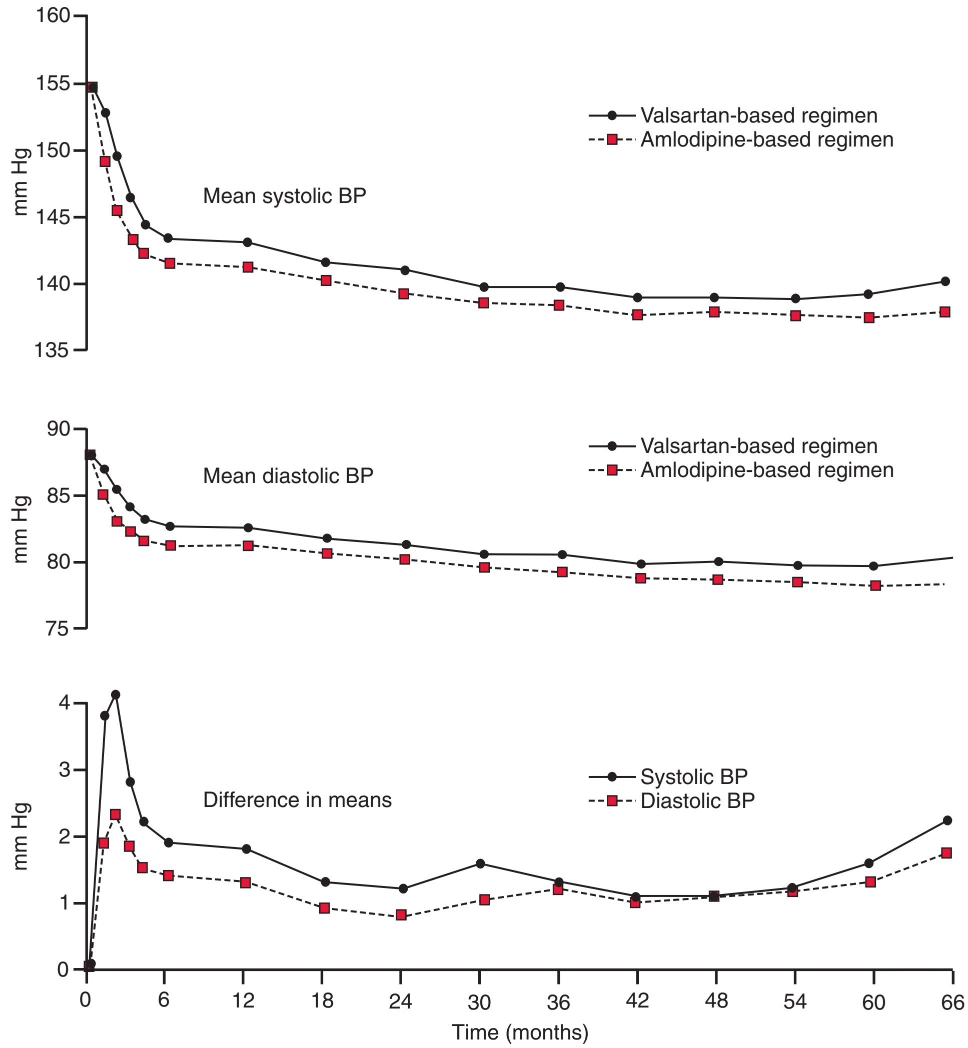


Figure 5–5 **Systolic and diastolic BP and differences (valsartan-amlodipine) in BP between treatment groups during follow-up.** BP difference between the two groups in the VALUE trial was significant (<0.0001) at every time point favoring the amlodipine-based regimen. Overall differences in systolic BP = 2.23 mm Hg (SE 0.18); overall differences in diastolic BP = 1.59 mm Hg (SE 0.11). (Redrawn with permission from Julius S, Kjeldsen V, Weber M, et al., for the VALUE trial group: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. Lancet 2004;363:2024.)

lower infarction rate based on our current understanding of the pathophysiology of acute coronary syndromes. Based on these two completed studies of the ACE inhibitors and angiotensin receptor blockers (ARBs), both in hypertensive patients at high risk for cardiovascular events that were neutral or slightly favorable compared with a diuretic, ACE inhibitors and angiotensin receptor blockers, it is hoped that these unfortunate accusations against a class of cardiovascular agents, when only a few were responsible, finally can be closed.

The issue of choice of antihypertensive agents and risk of new onset diabetes has now also favored calcium channel blockers as neutral agents compared with diuretics and β-blockers. However, ACE inhibitors and angiotensin receptor blockers reverse the insulin resistance in this arena. The efficacy of blood pressure control and the efficacy with dihydropyridines such as amlodipine indicate that it is likely these agents will play an important role in combination with renin-angiotensin-aldosterone system (RAAS) inhibitors because of their efficacy in blood pressure lowering and their demonstrated safety.

β-ADRENERGIC BLOCKERS

β-Blockers, which constitute a major pharmacotherapeutic advance, were conceived initially for the treatment of patients with angina pectoris and arrhythmias; however, they also have therapeutic effects in many other clinical disorders, including systemic hypertension, hypertrophic cardiomyopathy, congestive cardiomyopathy,[76] mitral valve prolapse, silent myocardial ischemia, migraine, glaucoma, essential tremor, and thyrotoxicosis. β-Blockers have been effective in treating unstable angina and reducing the risks of cardiovascular death and nonfatal reinfarction in patients who have survived an acute MI.[77] β-Adrenergic receptor blockade is also a potential treatment modality, with and without fibrinolytic therapy, to reduce the extent of myocardial injury and death during the hyperacute phase of MI.

β-Adrenergic Receptors

The effects of an endogenous hormone or exogenous drug depend ultimately on physiochemical interactions with macromolecular structures of cells called *receptors*. *Agonists* interact with a receptor and elicit a response; *antagonists* interact with receptors and prevent the action of agonists.

In the case of catecholamine action, the circulating hormone or drug ("first messenger") interacts with its specific receptor on the external surface of the target cells. The drug hormone/receptor complex, mediated by the G protein G_s, activates the enzyme adenyl cyclase on the internal surface of the plasma membrane of the target cell, which accelerates the intracellular formation of cAMP. cAMP-dependent protein kinase ("second messenger") then stimulates or inhibits various metabolic or physiological processes.[78-80] Catecholamine-induced increases in intracellular cAMP are usually associated with the stimulation of β-adrenergic receptors, whereas α-adrenergic receptor stimulation is mediated by G protein G_i and is associated with lower concentrations of cAMP, and possibly increased amounts of GMP in the cell. These different receptor effects may result in the production of opposing physiological actions from catecholamines, depending on which adrenergic receptor system is activated.

Most research on receptor action previously bypassed the initial binding step and the intermediate steps and examined either the accumulation of cAMP or the end step, the physiological effect. Radioactive agonists or antagonists (radioligands) that attach to and label the receptors have been used to study binding and hormone action.[79-81] The cloning of adrenergic receptors has also revealed important clues about receptor function.[79]

In contrast to the older concept of adrenergic receptors as static entities in cells, which simply serve to initiate the chain of events, newer theories hold that the adrenergic receptors are subject to a wide variety of controlling influences that result in dynamic regulation of adrenergic receptor sites or their sensitivity to catecholamines, or both.[82] Changes in tissue concentration of receptor sites are probably involved in mediating important fluctuations in tissue sensitivity to drug action.[80,81,83] These principles may have significant clinical and therapeutic implications. For example, an apparent increase in the number of β-adrenergic receptors, and thus a supersensitivity to agonists, may be induced by chronic exposure to antagonists.[80,83] With prolonged adrenergic receptor blocker therapy, receptor occupancy by catecholamines can be diminished and the number of available receptors can be increased.[83] When the β-adrenergic receptor blocker is withdrawn suddenly, an increased pool of sensitive receptors is available for endogenous catecholamine stimulation. The resultant adrenergic stimulation may precipitate unstable angina pectoris, an MI, or both.[84] Specific gene polymorphisms of both the β_1 and β_2 receptors may also influence the pharmacologic response to β-blocking agents.[85]

Effects in Angina Pectoris

Ahlquist[86] demonstrated that sympathetic innervation of the heart causes the release of norepinephrine, activating β-adrenergic receptors in myocardial cells. This adrenergic stimulation causes an increment in heart rate, isometric contractile force, and maximal velocity of muscle fiber shortening, all of which lead to an increase in cardiac work and myocardial oxygen consumption.[87] The decrease in intraventricular pressure and volume caused by the sympathetic mediated enhancement of cardiac contractility tends to reduce myocardial oxygen consumption by reducing myocardial wall tension (LaPlace law).[88] Although there is a net increase in myocardial oxygen demand, this is normally balanced by an increase in coronary blood flow. Angina pectoris is believed to occur when oxygen demand exceeds supply (i.e., when coronary blood flow is restricted by coronary atherosclerosis).[58,89] Because the conditions that precipitate anginal attacks (e.g., exercise, emotional stress, food) cause an increase in cardiac sympathetic activity, it might be expected that blockade of cardiac β-adrenergic receptors would relieve anginal symptoms. It is on this basis that the early clinical studies with β-blocking drugs in patients with angina pectoris were initiated.[90]

Three main factors—heart rate, ventricular systolic pressure, and the size of the left ventricle-contribute to the myocardial oxygen requirements of the left ventricle. Of these, heart rate and systolic pressure appear to be important (the product of heart rate multiplied by the systolic blood pressure is a reliable index for predicting the precipitation of angina in a given patient).[91,92] However, myocardial contractility may be even more important.[93]

The reduction in heart rate effected by β-blockade has two favorable consequences: (l) a decrease in blood pressure, thus reducing myocardial oxygen needs; and (2) a longer diastolic filling time associated with a slower heart rate, allowing for increased coronary perfusion.[93] β-blockade also reduces exercise-induced blood pressure increments, the velocity of cardiac contraction, and oxygen consumption at any patient's workload (Table 5–5).[91,92] After treatment, a reduced heart rate variability, a marker for abnormal autonomic control of the heart, or low exercise tolerance may predict those patients who will respond best to treatment with β-blockade.[93-95] Despite the favorable effects on heart rate, the blunting of myocardial contractility with β-blockers may be the primary mechanism of their antianginal benefit.[93,96] In normal human coronary arteries, β_2-adrenergic receptor-mediated vasodilatation enhances coronary perfusion, an effect that is impaired by severe atherosclerosis.[97]

Studies in dogs have shown that propranolol causes a decrease in coronary blood flow.[98] However, subsequent experimental animal studies have demonstrated that β-blocker-induced shunting occurs in the coronary circulation, maintaining blood flow to ischemic areas, especially in the subendocardial region.[99] In humans, concomitant with the decrease in myocardial oxygen consumption, β-blockers can cause a reduction in coronary blood flow and an increase in coronary vascular resistance.[100] On the basis of coronary autoregulation, the overall reduction in myocardial oxygen needs with β-blockers may be sufficient cause for this clinically tolerated decrease in coronary blood flow.[92]

Virtually all β-blockers, regardless of whether they have partial agonist activity, α-adrenergic receptor-blocking effects, membrane-stabilizing activity, or general or selective β-blocking properties, produce some degree of increased work capacity without pain in patients with angina pectoris. Therefore, it must be concluded that this results from their common property: blockade of cardiac β-adrenergic receptors (Table 5–6). Both D- and L-propranolol have membrane-stabilizing activity, but only L-propranolol has significant β-blocking activity. The racemic mixture (D,L-propranolol) causes decreases in both heart rate and force of contraction in dogs, whereas the D-isomer has hardly any β-adrenergic receptor-blocking effect. In humans, D-propranolol, which has "membrane" activity but no β-blocking properties, has been found to be ineffective in relieving angina pectoris even at very high doses.[101]

Although exercise tolerance improves with β-blockade, the increments in heart rate and blood pressure with exercise are blunted, and the rate-pressure product (systolic blood pressure multiplied by heart rate) achieved when pain occurs is lower than that reached during a control run.[102] The depressed pressure-rate product at the onset of pain (about 20% reduction from control) is reported to occur with various β-blockers, probably related to decreased cardiac output and possibly a decrease in coronary perfusion. Thus, although there is increased exercise tolerance with β-blockade, patients exercise less than might be expected. This may also relate to the action of β-blockers in increasing LV size, causing increased LV wall tension and an increase in oxygen consumption at a given blood pressure.

Table 5–5 Possible Mechanisms by Which β-Adrenergic-Blocking Agents Protect the Ischemic Myocardium

- Reduction in myocardial consumption, heart rate, blood pressure, and myocardial contractility
- Augmentation of coronary blood flow, increase in diastolic perfusion time by reducing heart rate, augmentation of collateral blood flow, and redistribution of blood flow to ischemic areas
- Prevention of and/or attenuation of atherosclerotic plaque rupture and subsequent coronary thrombosis
- Alterations in myocardial substrate utilization
- Decrease in microvascular damage
- Stabilization of cell and lysosomal membranes
- Shift of oxyhemoglobin dissociation curve to the right
- Inhibition of platelet aggregation
- Inhibition of myocardial apoptosis, allowing natural cell regeneration to occur

From Frishman WH: Alpha and beta-adrenergic blocking drugs. In Frishman WH, Sonnenblick EH, Sica DA (eds): Cardiovascular Pharmacotherapeutics, 2nd ed. New York, McGraw-Hill, 2003, pp 67-97.

Comparison with Other Antianginal Therapies

In a meta-analysis of clinical trial experience over 20 years that compared β-blockers, CCBs, and nitrates in patients who had stable angina pectoris, it was demonstrated that β-blockers provide an equivalent reduction in angina and lead to similar or reduced rates of adverse experiences compared with either CCBs or long-acting nitrates.[53,68,103,104] The rates of cardiac death and MI were not significantly different for β-blockers than for CCBs.

Angina at Rest and Vasospastic Angina

Angina pectoris can be caused by multiple mechanisms, including coronary vasospasm, myocardial bridging, and thrombosis, which appear to be responsible for ischemia in a significant proportion of patients with unstable angina and angina at rest.[68,91-106] Therefore, because β-blockers primarily reduce myocardial oxygen consumption but fail to exert vasodilating effects on coronary vasculature, they may not be totally effective in patients in whom angina is caused or increased by dynamic alterations in coronary luminal diameter.[91] Despite potential dangers in rest and vasospastic angina, β-blockers have been used successfully as monotherapy and in combination with vasodilating antianginal agents in the majority of patients. In addition, there is now evidence that β-blockers can reduce C-reactive protein levels, an inflammatory marker of increased cardiovascular morbidity and mortality.[107]

Combined Use of β-Blockers with Other Antianginal Therapies in Angina Pectoris

Nitrates. As noted earlier, combined therapy with nitrates and β-blockers may be more efficacious for the treatment of angina pectoris than the use of either drug alone.[58,91,105] The primary effects of β-blockers are to cause a reduction in both resting heart rate and the response of heart rate to exercise. Because nitrates produce a reflex increase in heart rate and contractility due to a reduction in arterial pressure, concomitant β-blocker therapy is extremely effective because it blocks this reflex increment in the heart rate. Similarly, the preservation of diastolic coronary blood flow with a reduced heart rate will also be beneficial.[91] In patients with a propensity for myocardial failure who may have a slight increase in heart size

Table 5–6 Pharmacodynamic Properties and Cardiac Effects of β-Adrenergic-Blocking Drugs

Drug	Relative β_1 Selectivity*	ISA	MSA	Resting HR	Exercise HR	Resting Myocardial Contractility	Resting BP	Exercise BP	Resting AV Conduction	Antiarrhythmic Effect
Acebutolol	+	+	+	↓↔	↓	↓	↓	↓	↓	+
Atenolol	++	0	0	↓	↓	↓	↓	↓	↓	+
Betaxolol	++	0	+	↓	↓	↓	↓	↓	↓	+
Bisoprolol†	++	0	0	↓	↓	↓	↓	↓	↓	+
Carteolol	0	+	0	↓↔	↓	↓↔	↓	↓	↓	+
Carvedilol‡	0	0	++	↓↔	↓	↓↔	↓	↓	↓↔	+
Esmolol	++	0	0	↓	↓	↓	↓	↓	↓	+
Labetalol§	0	+	0	↓↔	↓	↓↔	↓	↓↓	↓↔	+
Metoprolol	++	0	0	↓	↓	↓	↓	↓	↓	+
Nadolol	0	0	0	↓	↓	↓	↓	↓	↓	+
Nebivolol¶¶	++	0	0	↓	↓	↓↔	↓	↓	↓	+
Oxprenolol	0	+	+	↓↔	↓	↓↔	↓	↓	↓↔	+
Penbutolol	0	+	0	↓↔	↓	↓↔	↓	↓	↓↔	+
Pindolol	0	++	+	↓↔	↓	↓↔	↓	↓	↓↔	+
Propranolol	0	0	++	↓	↓	↓	↓	↓	↓	+
Isomer-D-propranolol	0	0	++	↔	↔	↔↓¶	↔	↔	↔↓¶	+
Sotalol	0	0	0	↓	↓	↓	↓	↓	↓	+
Timolol	0	0	0	↓	↓	↓	↓	↓	↓	+

*β_1 Selectivity is seen only with low therapeutic drug concentrations. With higher concentrations, β_1 selectivity is not seen.
†Bisoprolol is also approved as a first-line antihypertensive therapy in combination with a very low-dose diuretic.
‡Carvedilol has peripheral vasodilating activity and additional α_1-adrenergic-blocking activity.
§Labetalol has additional α_1-adrenergic-blocking activity and direct vasodilatory activity.
¶¶Nebivolol has additional actions to increase endothelium-dependent vasodilation by increasing the activity of nitric oxide
¶Effects of D-propranolol with doses in humans well above the therapeutic level. The isomer also lacks β-blocking activity.
AV, atrioventricular; BP, blood pressure; HR, heart rate; ISA, intrinsic sympathomimetic activity; MSA, membrane stabilizing activity; ++, strong effect; +, modest effect; 0, absent effect; ↓, reduction; ↔, no change.
Adapted from Frishman WH: Clinical Pharmacology of the β-Adrenoceptor Blocking Drugs, 2nd ed. Norwalk, Conn, Appleton-Century-Crofts, 1984, p 15.

with the β-blockers, the nitrates will counteract this tendency by reducing heart size as a result of its peripheral venodilator effects. During the administration of nitrates, the reflex increase in contractility that is mediated through the sympathetic nervous system will be blunted by the presence of β-blockers. Similarly, the increase in coronary resistance associated with β-blocker administration can be ameliorated by the administration of nitrates.[91]

Calcium Channel Blockers. Some CCBs (diltiazem, verapamil) also slow the heart rate and inhibit AV nodal conduction. Combined therapy with β-blockers and CCBs can provide clinical benefits for patients with angina pectoris who remain symptomatic with the use of either agent alone.[108-111] Because adverse cardiovascular effects can also occur with combination treatment, such as heart block and excessive myocardial depression, patients being considered for such treatment must be carefully selected and observed.[108,109]

Hemodynamically, these two types of agents have different effects on the circulation (see Tables 5–3 and 5–6), leading to the possibility of therapeutic combination. Of the combinations, β-blockade plus a DHP, such as nifedipine, is likely to be simplest. The DHPs do not inhibit the SA or AV node and, therefore, can be more readily combined with a β-blocker than can the non-DHPs, such as verapamil and diltiazem. Because the tendency to produce tachycardia with the DHPs is antagonized by the β-blocker, there are no additive effects on the SA or AV node, and through vasodilatation, including coronary vasodilatation, the DHPs can contribute to the antianginal effect. β-Blockade should be combined with the non-DHPs such as verapamil and diltiazem only after consideration of the risks and plans are in place for patient monitoring. With non-DHP CCBs, there is the risk of extreme bradycardia, AV nodal block, or a marked negative inotropic effect. Second-generation CCBs, such as the DHPs amlodipine, felodipine, isradipine, and nicardipine, can also be readily combined with β-blockade.

Ranolazine. The FDA has approved extended-release ranolazine for the treatment of chronic angina in patients who have not achieved an adequate response with other antianginal drugs. Ranolazine's antianginal and anti-ischemic mechanism of action is not known. It should be used in combination with a β-blocker and/or a nitrate (see Appendix 1).[111a,b]

Conditions Associated with Angina Pectoris

Arrhythmias. β-Blockers are an important treatment modality for various cardiac arrhythmias, especially in patients with ischemic heart disease. Although it was initially believed that β-blockers were more effective in treating supraventricular arrhythmias than ventricular arrhythmias, subsequent studies suggest that this may not be the case.[112,113] β-Blockers can be quite useful in the prevention and treatment of ventricular tachyarrhythmias in the setting of myocardial ischemia, mitral valve prolapse, the hereditary QT interval prolongation syndrome, and other cardiovascular conditions, such as cardiomyopathy.[112-122] β-Blockers can be combined with amiodarone with relative safety and synergy of antiarrhythmic action,[123] as well as with implantable cardioverter-defibrillators to reduce the frequency of shocks.[124]

Hypertension. The mechanism of the antihypertensive effect of β-blockade is still under dispute.[125,126] Its effect on overall cardiovascular mortality appears to be similar to other classes of antihypertensive drugs.[127] Initially, β-blockers decrease the heart rate, and cardiac output falls by about 20%, yet the blood pressure does not fall because the arteriolar resistance reflexively increases. Within 24 hours of the start of β-blocker treatment, the peripheral resistance starts to fall, so arterial pressure declines. The mechanism of this delayed hypotensive effect is unclear, but it is thought to involve inhibition of prejunctional β-adrenergic receptors.[128] Alternatively, inhibition of the renin-angiotensin system may account for the delayed vasodilatation.[129] Additional antihypertensive mechanisms may involve a central action and decreased renin release.

Survivors of Acute Myocardial Infarction. β-Blockers have beneficial effects on many determinants of myocardial ischemia (see Table 5–5 and Chapter 11).[77,92,130] The results of placebo-controlled, long-term treatment trials with some β-blockers in survivors of acute MI demonstrated a favorable effect on total mortality rates; cardiovascular mortality rates, including sudden and nonsudden cardiac deaths; and the incidence of nonfatal reinfarction. Patients in these studies included those who had relative contraindications to β-blockade but still appeared to benefit[131] and diabetic patients who also responded favorably to treatment.[132] The beneficial results of β-blocker therapy can be explained by both the antiarrhythmic and the anti-ischemic effects of these drugs.[92,116,133-136] It has also been proposed that β-blockers reduce the risk of atherosclerotic plaque fissure and subsequent thrombosis.[137] Two nonselective β-blockers, propranolol and timolol, are approved for use in reducing the risk of death in MI survivors when started 5 to 28 days after an MI. Metoprolol and atenolol, two β_1-selective blockers, are approved for the same indication, and both can be used intravenously in the hyperacute phase of an MI. β-Blockers have also been suggested as a treatment to reduce the extent of myocardial injury[138-140] and deaths during the hyperacute phase of MI.[141-144] The α/β-blocker carvedilol is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of myocardial infarction and have a left ventricular ejection fraction of <40% (with or without symptomatic heart failure).[145] Intravenous and oral atenolol have been shown to be effective in causing a modest reduction in early mortality rates when administered during the hyperacute phase of acute MI.[141] Atenolol and metoprolol reduce early infarct mortality rates by 15%,[141,142] an effect that may be improved on when β-blockade is combined with thrombolytic therapy.[146] Despite all of the evidence showing that β-blockers are beneficial in patients who survive MI,[147-150] they are still considerably underused in clinical practice.[151-155]

"Silent" Myocardial Ischemia. Investigators have observed that not all myocardial ischemic episodes detected on electrocardiography are associated with detectable symptoms.[156] Positron emission imaging techniques validated the theory that these silent ischemic episodes are indicative of true myocardial ischemia.[157] Compared with symptomatic ischemia, the prognostic importance of silent myocardial ischemia that occurs at rest or during exercise has not been determined. β-Blockers are as successful in reducing the frequency and timing of silent ischemic episodes detected by ambulatory electrocardiographic monitoring as they are in reducing the frequency of painful ischemic events.[157-161]

Other Cardiovascular Conditions Associated with Angina Pectoris

Although β-blockers have been studied extensively in patients with angina pectoris, arrhythmias, and hypertension, they

have also been shown to be safe for other cardiovascular conditions associated with angina pectoris.

Hypertrophic Cardiomyopathy. β-Blockers without partial agonist activity have been proved to be effective for patients with hypertrophic cardiomyopathy.[162,163] These drugs are useful for reducing dyspnea, angina, and syncope.[130,164] β-Blockers have also been shown to lower the intraventricular pressure gradient both at rest and with exercise.

The outflow pressure gradient is not the only abnormality in hypertrophic cardiomyopathy; more important is the loss of ventricular compliance, which impedes normal LV function. It has been shown through both invasive and noninvasive methods that propranolol can improve LV function in this condition.[165] The drug also produces favorable changes in ventricular compliance while it relieves symptoms. Propranolol has been approved for this condition and may be combined with the CCB verapamil or disopyramide in patients who do not respond to the β-blocker alone.

The salutary hemodynamic and symptomatic effects produced by β-blockers derive from their inhibition of sympathetic stimulation of the heart.[166] There is no evidence that the drug alters the primary cardiomyopathic process; many patients remain in or return to their severely symptomatic state, and some patients die despite their administration.[162,163]

Congestive Cardiomyopathy. The ability of intravenous sympathomimetic amines to effect an acute increase in myocardial contractility through stimulation of the β-adrenergic receptor had prompted the hope that the use of oral catecholamine analogs could provide long-term benefit for patients with severe heart failure. However, observations concerning the regulation of the myocardial adrenergic receptor and abnormalities of β-adrenergic receptor-mediated stimulation of the failing myocardium have caused a critical reappraisal of the scientific validity of sustained β-adrenergic receptor stimulation.[146,167-169] Evidence suggests that β-adrenergic receptor blockade may, when tolerated, have a favorable effect on the underlying cardiomyopathic process.[170]

Enhanced sympathetic activation is seen consistently in patients with congestive heart failure and is associated with decreased exercise tolerance,[171] hemodynamic abnormalities,[172] and increased mortality rates.[173] Increases in sympathetic tone can potentiate the renin-angiotensin system in patients, leading to increased salt and water retention, arterial and venous constriction, and increments in ventricular preload and afterload.[170] Elevated levels of catecholamines can increase heart rate and cause coronary vasoconstriction.[92] They can adversely influence myocardial contractility on the cellular level,[174,175] while causing myocyte hypertrophy[175,176] and vascular remodeling. Catecholamines can stimulate growth and provoke oxidative stress in terminally differentiated cardiac cells; these two factors can trigger the process of programmed cell death known as *apoptosis*.[177,178] Finally, they can increase the risk of sudden death in patients with congestive heart failure by adversely influencing the electrophysiologic properties of the failing heart.[179]

Controlled trials with several different β-blockers in patients with either ischemic or nonischemic cardiomyopathy showed that these drugs improve symptoms, ventricular function, and functional capacity, while reducing the need for hospitalization.[76,180,181] A series of placebo-controlled clinical trials with the α-β-blocker carvedilol[182] and the β_1-selective agents bisoprolol and metoprolol[183-185] have shown a mortality benefit in patients with New York Heart Association functional class II to IV heart failure when the drug was used in addition to diuretics, ACE inhibitors, and digoxin. For patients with class II to III heart failure, initial treatment with a β-blocker followed by an ACE inhibitor was found to be at least as effective as beginning with an ACE inhibitor.[186]

The mechanisms of benefit with β-blocker use are not yet known. Possible mechanisms for β-blocker benefit in chronic heart failure include the upregulation of impaired β-adrenergic receptor expression in the heart[146,187,188] and an improvement in impaired baroreceptor functioning, an effect that can inhibit excess sympathetic outflow.[170] It has been suggested that long-term therapy with β-blockers improves the left atrial contribution to LV filling[189] while increasing the levels of cardiac natriuretic peptides.[190,191]

Mitral Valve Prolapse. Atypical chest pain, malignant arrhythmias, and nonspecific ST- and T-wave abnormalities have been observed with this condition. By decreasing sympathetic tone, β-blockers have been shown to be useful for relieving the chest pains and palpitations that many of these patients experience and for reducing the incidence of life-threatening arrhythmias and other electrocardiographic abnormalities.[192]

Dissecting Aneurysms. β-Blockade plays a major role in the treatment of patients with acute aortic dissection. During the hyperacute phase, β-blockers reduce the force and velocity of myocardial contraction (dP/dT) and, hence, the progression of the dissecting hematoma.[193] Moreover, β-blockade should be initiated simultaneously with the institution of other antihypertensive therapy (e.g., SNP) that may cause reflex tachycardia and increases in cardiac output, factors that can aggravate the dissection process. β-Blockade is administered intravenously to reduce the heart rate to below 60 beats/min. Once a patient is stabilized (i.e., adequate control of heart rate and blood pressure and no further pain from dissection) and long-term medical management is contemplated, the patient should be maintained on oral β-blocker therapy to prevent the recurrence of dissection.[193]

Syndrome X. A dysfunction of small coronary arterial vessels has been hypothesized to be responsible for syndrome X, a chest pain syndrome often presenting without evidence of large-vessel coronary artery disease. The treatment of syndrome X, however, remains largely empiric and often unsatisfactory. Some investigators found that β-blockers rather than CCBs and nitrates were useful in relieving symptoms,[194] suggesting that they may be the preferred drugs when starting pharmacologic treatment for this condition.

Perioperative Therapy in High-Risk Patients with Ischemic Heart Disease. Cardiovascular complications are the most important causes of perioperative complications and death in high-risk patients undergoing major vascular and nonvascular surgical procedures. β-Blocker treatment before surgery reduces the perioperative incidence of death from cardiac causes and nonfatal MI.[131,195-197]

Pharmacologic Differences Among β-Adrenergic Receptor-Blocking Drugs

More than 100 β-blockers have been synthesized, and more than 30 are available worldwide for clinical use.[91] Selectivity for two subgroups of the β-adrenergic receptor population has been prominent in the development of β-blockers: β_1-adrenergic receptors in the heart and β_2-adrenergic receptors in the peripheral circulation and bronchi.[91,198] More

controversial has been the introduction of β-blockers with α-adrenergic receptor-blocking actions, varying amounts of selective and nonselective intrinsic sympathomimetic activity (partial agonist activity), CCB activity, nitric oxide potentiating action, and nonspecific membrane-stabilizing effects (Table 5–7).[164] There also are pharmacokinetic differences among β-blockers that may be of clinical importance.[198]

Fifteen β-blockers are marketed in the United States for cardiovascular disorders: *propranolol* for angina pectoris, arrhythmias, systemic hypertension, migraine prophylaxis, essential tremor, and hypertrophic cardiomyopathy and to reduce the risk of cardiovascular death in survivors of an acute MI; *nadolol* for hypertension and angina pectoris; *timolol* for hypertension and to reduce the risk of cardiovascular death and nonfatal reinfarction in survivors of MI and in a topical form for glaucoma; *atenolol* and *metoprolol* for hypertension and angina and in intravenous and oral formulations to reduce the risk of cardiovascular death in survivors of MI; *penbutolol*, *bisoprolol*, *pindolol*, and *carvedilol* for hypertension; *betaxolol* and *carteolol* for hypertension and in a topical form for glaucoma; *acebutolol* for hypertension and ventricular arrhythmias; intravenous *esmolol* for supraventricular arrhythmias; *sotalol* for atrial and ventricular arrhythmias; and *labetalol* for hypertension and in an intravenous form for hypertensive emergencies.[164,198-203] *Carvedilol*, *metoprolol*, and *bisoprolol* are approved for clinical use in the treatment of congestive heart failure. Nebivolol, a β_1-selective agent with nitric oxide potentiating action, is now under review by the FDA for clinical use in hypertension.[204]

Despite the extensive experience with β-blockers in clinical practice, there have been no studies suggesting that any of these agents have major advantages or disadvantages compared with the others for the treatment of many cardiovascular diseases. When any available β-blocker is titrated properly, it can be effective in patients with arrhythmia, hypertension, or angina pectoris (see Table 5–7).[164,198-203] However, one agent may be more effective than other agents in reducing adverse reactions in some patients and in managing specific situations.

Potency

β-Blockers are competitive inhibitors of catecholamine binding at β-adrenergic receptor sites. The dose-response curve of the catecholamine is shifted to the right; that is, a given tissue response requires a higher concentration of agonist in the presence of β-blockers.[130] β_1-Blocking potency can be assessed by the inhibition of tachycardia produced by isoproterenol or exercise (the more reliable method in the intact organism); potency varies among compounds.[130] These differences in potency are of no therapeutic relevance; however, they do explain the different drug doses needed to achieve effective β-blockade when initiating therapy in patients or when switching from one agent to another.[198,205,206]

β_1-Selectivity

β-Blockers may be classified as *selective* or *nonselective* according to their relative abilities to antagonize the actions of sympathomimetic amines in some tissues at lower doses than those required in other tissues.[198,199,205,206] When used in low doses, β_1-selective blockers such as acebutolol, betaxolol, bisoprolol, esmolol, atenolol, and metoprolol inhibit cardiac β_1-adrenergic receptors but have less influence on bronchial and vascular β-adrenergic receptors (β_2). In higher doses, however, β_1-selective blockers also block β_2-adrenergic receptors. Accordingly, β_1-selective agents may be safer than nonselective ones in patients with obstructive pulmonary disease, because β_2-adrenergic receptors remain available to mediate adrenergic bronchodilatation.[207] Even relatively selective β-blockers may aggravate bronchospasm in certain patients, so these drugs should generally not be used in patients with active bronchospastic disease.

A second theoretical advantage is that, unlike nonselective β-blockers, β_1-selective blockers in low doses may not block the β_2-adrenergic receptors that mediate the dilatation of arterioles. During the infusion of epinephrine, nonselective β-blockers can cause a pressor response by blocking β_2-adrenergic receptor-mediated vasodilatation, because β-adrenergic vasoconstrictor receptors are still operative. Selective β_1-blockers may not induce this pressor effect in the presence of epinephrine and may lessen the impairment of peripheral blood flow. It is possible that leaving the β_2-adrenergic receptors unblocked and responsive to epinephrine may be functionally important in some patients with asthma, hypoglycemia, hypertension, or peripheral vascular disease who are treated with β-blockers.[164,198,199]

Intrinsic Sympathomimetic Activity (Partial Agonist Activity)

Certain β-blockers possess intrinsic sympathomimetic activity (partial agonist activity) at β_1-adrenergic receptor sites, β_2-adrenergic receptor sites, or both. In a β-blocker, this property is identified as a slight cardiac stimulation that can be blocked by propranolol.[164,198,202] The β-blockers with this property partially activate the β-adrenergic receptor in addition to preventing the access of natural or synthetic catecholamines to the receptor. Dichloroisoprenaline, the first β-adrenergic receptor-blocking drug to be synthesized, exerted such marked partial agonist activity that it was unsuitable for clinical use. However, compounds with less partial agonist activity are effective β-blockers. The partial agonist effects of β-blockers such as pindolol differ from those of the agonists epinephrine and isoproterenol in that the maximum pharmacologic response that can be obtained is low, although the affinity for the receptor is high. In the treatment of patients with arrhythmias, angina pectoris of effort, and hypertension, drugs with mild-to-moderate partial agonist activity appear to be as efficacious as are β-blockers that lack this property. It is still debated whether the presence of partial agonist activity in a β-blocker constitutes an overall advantage or disadvantage in cardiac therapy.[202] Drugs with partial agonist activity cause less slowing of the heart rate at rest than do propranolol and metoprolol, although the increments in heart rate with exercise are similarly blunted. These β-blockers reduce peripheral vascular resistance and may cause less depression or AV conduction than drugs that lack these properties.[202,208] Some investigators claim that partial agonist activity in a β-blocker protects against myocardial depression, adverse lipid changes, bronchial asthma, and peripheral vascular complications, as caused by propranolol.[202,208-210]

Table 5–7 Properties of Various β-Adrenoceptor Antagonist Agents: Noncardioselective Versus Cardioselective and Vasodilatory Agents

Generic Name (Trade Name)	ISA	Plasma Half-Life	Lipid* Solubility	First-Pass Effect	Loss by Liver/Kidney	Plasma Protein Binding (%)	Usual Dose for Angina (Other Indications)	Usual Doses as Sole Therapy for Mild/Moderate Hypertension
Noncardioselective								
Propranolol†‡ (Inderal)	–	1-6	+++	++	Liver	90	80 mg bid usually adequate (may give 160 mg bid)	Start with 10-40 mg bid.; mean 160-320 mg/day, 1 or 2 doses
(Inderal LA)	–	8-11	+++	++	Liver	90	80-320 mg qd	80-320 mg daily
(Innopran XL)	–	8-11	+++	++	Liver	90	Not indicated	80-120 mg hs (at bedtime)
Carteolol† (Cartrol)	+	5-6	0/+	0	Kidney	20-30	Not evaluated	2.5-10 mg single dose
Nadolol†‡ (Corgard)	–	20-24	0	0	Kidney	30	40-80 mg qd; up to 240 mg	40-80 mg daily; up to 320 mg
Penbutolol† (Levatol)	+	20-25	+++	++	Liver	98	Not studied	10-20 mg daily
Sotalol§ (Betapace; Betapace AF)	–	7-18 (mean 12)	0	0	Kidney	5	80-240 mg bid in two doses for serious ventricular arrhythmias; up to 160 mg bid for atrial fibrillation, flutter	80-320 mg/day; mean 190 mg per day
Timolol† (Blocadren)	–	4-5	+	+	Liver, kidney	60	10 mg bid after MI	10-20 mg bid
Cardioselective								
Acebutolol† (Sectral)	++	8-13	0		Liver, kidney	15	400-1200 mg/day in two doses for PVCs	400-1200 mg/day; can be given as a single dose
Atenolol†‡ (Tenormin)	–	6-7	0	0	Kidney	10	50-200 mg qd	50-100 mg daily
Betaxolol† (Kerlone)	–	14-22	++	++	Liver, kidney	50	–	10-20 mg daily
Bisoprolol† (Zebeta)	–	9-12	+	0	Liver, kidney	30	10 mg qd (not in the U.S.)	2.5-40 mg daily
Metoprolol†‡ (Lopressor)		3-7	+	++	Liver	12	50-200 mg bid	100-400 mg/day in 1 or 2 doses
(Toprol-XL)		(slow release)	+	++	Liver	12	100-400 mg qd	As above, 1 dose

continued

Table 5–7 Properties of Various β-Adrenoceptor Antagonist Agents: Noncardioselective Versus Cardioselective and Vasodilatory Agents—cont'd

Generic Name (Trade Name)	ISA	Plasma Half-Life	Lipid* Solubility	First-Pass Effect	Loss by Liver/Kidney	Plasma Protein Binding (%)	Usual Dose for Angina (Other Indications)	Usual Doses as Sole Therapy for Mild/Moderate Hypertension
Vasodilatory β-Blockers, Noncardioselective								
Labetalol† (Trandate, Normodyne)	–	6-8	+++	++	Liver, some kidney	90	As for hypertension	300-600 mg/day in 3 doses; top dose 2400 mg/day
Pindolol† (Visken)	$\beta_1\beta_2$	4	+	+	Liver, kidney	55	2.5-7.5 mg tid (not in the U.S.)	5-30 mg in two daily doses
Carvedilol†¶ (Coreg)	–	6	+	++	Liver	95	In the U.S., U.K., licensed for heart failure up to 25 mg bid; start with low dose	12.5-25 mg bid
Vasodilatory β-Blockers, Selective								
Nebivolol	–	6-10	++	++	Liver, kidney	98	2.5-10 mg qd	2.5-10 mg qd

*Octanol-water distribution coefficient (pH 7.4, 37°C) where 0 is ≤0.5; + is 0.5-2; ++ is 2-10; and +++ is ≥10.
†Approved by the U.S. Food and Drug Administration for hypertension.
‡Approved by the U.S. Food and Drug Administration for angina pectoris.
§Approved for life-threatening ventricular tachyarrhythmias.
¶Approved for heart failure.
ISA, intrinsic sympathomimetic activity; PVC, premature ventricular contraction.
Modified from Opie LH, Yusuf S: Beta-Blocking Agents. In Opie LH, Gersh BJ (eds): Drugs for the Heart, 5th ed. Philadelphia: WB Saunders, 2001, pp 1-32.

The evidence to support these claims is not conclusive, and more definitive clinical trials will be necessary to resolve these issues.

α-Adrenergic Activity

Labetalol is a β-blocker with antagonistic properties at both α- and β-adrenergic receptors, and it has direct vasodilator activity.[130,164,211] Labetalol has been shown to be 6 to 10 times less potent than phentolamine at α-adrenergic receptors, 1.5 to 4 times less potent than propranolol at β-adrenergic receptors, and is itself 4 to 16 times less potent at α- than at β-adrenergic receptors.[130,164,211] Like other β-blockers, it is useful in the treatment of hypertension and angina pectoris.[130,212,213] Unlike most β-blockers, however, the additional α-adrenergic receptor-blocking actions of labetalol lead to a reduction in peripheral vascular resistance that may maintain cardiac output.[130,211] Whether concomitant α-adrenergic receptor-blocking activity is actually advantageous in a β-blocker remains to be determined.

Carvedilol is another β-blocker with additional β-adrenergic receptor-blocking activity. Carvedilol has an α_1- to β-blockade ratio of 1:10. On a milligram-to-milligram basis, carvedilol is about 2 to 4 times more potent than propranolol as a β-blocker.[76] In addition, carvedilol has antioxidant and antiproliferative activities.[214] Carvedilol has been used for the treatment of hypertension and angina pectoris and is approved as a treatment for hypertension and for patients with symptomatic heart failure.[76,215]

Nitric Oxide Potentiating Effect

A novel aspect of the pharmacology of the β_1-selective antagonist nebivolol is its ability to produce endothelium-dependent vasodilation through a nitric oxide pathway. Nebivolol produces vasodilation by acting as a β_3-receptor agonist, which increases the activity of nitric oxide.[204] Nitric oxide activity is also augmented by nebivolol through the prevention of nitric oxide deactivation.[204] The nitric oxide-mediated vasodilatory effects of nebivolol occur primarily in the small arteries, which contributes to the effect of the drug on arterial blood pressure.[204]

Pharmacokinetics

Although the β-blockers as a group have similar therapeutic effects, their pharmacokinetic properties are markedly different.[164,206,216,217] Their varied aromatic ring structures lead to differences in completeness or gastrointestinal absorption, amount of first-pass hepatic metabolism, lipid solubility, protein binding, extent of distribution in the body, penetration into the brain, concentration in the heart, rate of hepatic biotransformation, pharmacologic activity of metabolites, and renal clearance of a drug and its metabolites, which may influence the clinical usefulness of these drugs in some patients.[164,198,206,216,217] The desirable pharmacokinetic characteristics of β-blockers in general are a lack of major individual differences in bioavailability and in metabolic clearance of the drug and a rate of removal from active tissue sites that is slow enough to allow longer dosing intervals.[164,198]

The β-blockers can be divided by their pharmacokinetic properties into two broad categories: (1) those eliminated via hepatic metabolism, which tend to have relatively short plasma half-lives; and (2) those eliminated unchanged by the kidney, which tend to have longer half-lives.[198] Propranolol and metoprolol are both lipid soluble, are almost completely absorbed by the small intestine, and are largely metabolized by the liver. They tend to have more variable bioavailability and relatively short plasma half-lives.[164,199,206,217] A lack of correlation between the duration of clinical pharmacologic effect and plasma half-life may allow these drugs to be administered once or twice daily.[198]

In contrast, agents such as atenolol and nadolol are more water soluble, are incompletely absorbed through the gut, and are eliminated unchanged by the kidney.[200,201] They tend to have less variable bioavailability in patients with normal renal function, in addition to longer half-lives, allowing once-a-day dosing.[200,201] The longer half-lives may be useful in patients who find compliance with frequent β-blocker dosing to be a problem.[200]

Long-acting sustained-release preparations of propranolol and metoprolol are available. Studies have shown that long-acting propranolol and metoprolol can provide a much smoother curve of daily plasma levels than can comparable divided doses of conventional immediate-release formulations.[218-220] In addition, a delayed-release sustained-release formulation of propranolol is available that is designed to target early morning elevations in blood pressure and heart rate related to circadian rhythm.[221]

The specific pharmacokinetic properties of individual β-blockers (first-pass metabolism, active metabolites, lipid solubility, and protein binding) may be clinically important.[130] When drugs with extensive first-pass metabolism are taken by mouth, they undergo so much hepatic biotransformation that relatively little drug reaches the systemic circulation.[164,198,206] Depending on the extent of first-pass effect, an oral dose of β-blocker must be larger than an intravenous dose to produce the same clinical effects.[199,206] Some β-blockers are transformed into pharmacologically active compounds (acebutolol) rather than inactive metabolites.[222] The total pharmacologic effect depends on the amount of the drug administered and its active metabolites.[217] Characteristics of lipid solubility in a β-blocker have been associated with the ability of the drug to concentrate in the brain,[164,198] and many side effects of these drugs that have not been clearly related to β-blockade may result from their actions on the central nervous system (e.g., lethargy, mental depression, and hallucinations).[198,201] It is still not certain, however, whether drugs that are less lipid soluble cause fewer of these adverse reactions.[200,201,223,224]

There are genetic polymorphisms that can influence the metabolism of various β-blockers, including propranolol, metoprolol, timolol, and carvedilol.[225,226] A one-codon difference of cytochrome P450 2D6 may explain a significant proportion of interindividual variation in the pharmacokinetics of propranolol in Chinese subjects.[225] There is no effect of exercise on the pharmacokinetics of propranolol.[227]

Adverse Effects of β-Adrenergic Receptor Blockers

An evaluation of adverse effects is complex because of the use of different definitions of side effects, the kinds of patients studied, study design features, and different methods

of ascertaining and reporting adverse side effects among studies.[228-230] Overall, the types and frequencies of adverse effects attributed to various β-blocker compounds appear similar.[228,229] The side effect profiles resemble those seen with concurrent placebo treatments, attesting to the remarkable safety margin of β-blockers.[230]

Adverse effects of β-blockers are an exaggeration of the normal cardiac therapeutic effects resulting in excess bradycardia, AV nodal block, and excess negative inotropic effect. All β-blockers tend to promote bronchospasm, with low doses of β_1-selective agents being the least harmful. Cold extremities occur with both selective and nonselective agents,[231] yet agents with intrinsic sympathomimetic activity may provide a slightly better skin temperature than propranolol, at least during an acute study.[232] The adverse effects of all β-blockers on the peripheral circulation may be less marked than previously thought.[233,234]

Fatigue is a frequent side effect, again found particularly with propranolol, with less of an effect when a β_1-selective or vasodilatory blocker is used, so both central and peripheral hemodynamic mechanisms may be involved.[235] Although one double-blind study shows no difference between the effects of the β_1-selective agent atenolol and placebo,[231] exercise physiologists find that there is some impairment in peak exercise with all β-blockers.

Impotence is often reported by patients who receive β-blockers, who are, however, usually middle-aged men with atherosclerotic arterial disease.[236] In one study, erectile dysfunction occurred in 11% of patients administered a β-blocker for hypertension compared with 26% of these patients administered a diuretic and 3% of placebo-treated patients.[237]

An impaired quality of life found especially with propranolol[238] is theoretically ascribed to its lipid solubility and brain penetration. Yet, a variety of β-blockers other than propranolol and with different pharmacologic properties preserve quality of life in hypertensive patients.[239] Central effects of β-blockers are often subtle and not always explicable by the lipid penetration hypothesis.[240]

β-Blockers have effects on various metabolic parameters, including blood sugar and blood lipids. In a prospective cohort study of 12,550 nondiabetic individuals with hypertension, β-blockers were shown to increase the risk of developing type II diabetes, a finding not observed with thiazide diuretics, ACE inhibitors, or CCBs.[241] This increased risk of diabetes must be weighed against the proven benefits of β-blockers in reducing the risk of cardiovascular events in patients with ischemic heart disease. Studies are needed to determine whether the use of ACE inhibitors in conjunction with β-blockers might counteract the adverse effects of β-blockers with respect to glucose tolerance.[242] Carvedilol has been shown not to affect glycemic control, while improving some components of the metabolic syndrome relative to metoprolol in diabetic patients.[215]

Similarly, β-blockers without intrinsic sympathomimetic activity have been shown in hypertensive patients to decrease high-density lipoprotein cholesterol concentrations by 7% to 10% and raise triglyceride concentrations by 10% to 20%.[209,243,244] These small changes in lipids induced by β-blockers do not appear to diminish the beneficial effects of blood pressure lowering on morbidity and mortality rates from coronary heart disease and stroke.

Contraindications to β-Adrenergic Receptor Blockers

There are several absolute contraindications. Cardiovascular contraindications include severe bradycardia (heart rate of less than 40 beats/min), preexisting high-degree AV nodal block (PR interval of more than 0.24 second without a functioning pacemaker), overt LV failure (except when the β-blocker is administered initially at low doses and under supervision to patients already receiving diuretics, digoxin, and an ACE inhibitor), and active peripheral vascular disease with rest ischemia. Severe bronchospasm is an absolute contraindication, even to β-selective agents. Severe psychological depression is an important relative contraindication, particularly for propranolol.[223]

Overdosage

Suicide attempts and accidental overdosing with β-blockers are being described with increasing frequency. Because β-blockers are competitive pharmacologic antagonists, their life-threatening effects (bradycardia, myocardial and ventilatory failure) can be overcome with an immediate infusion of a β-agonist agent, such as isoproterenol or dobutamine.[245] In situations where catecholamines are not effective, intravenous glucagon, amrinone, or milrinone has been used.[245] There are no published recommended doses of intravenous catecholamines or phosphodiesterase inhibitors to treat β-blocker overdose. These agents should be used in their usual pharmacologic concentration until one is certain that reversal of β-blocker toxicity (reversal of heart blocks, excessive bradycardia, and myocardial depression) has occurred.

Monitoring of cardiorespiratory function is necessary for at least 24 hours in an intensive care unit after the patient responds to treatment of the β-blocker overdose. Patients who recover usually have no long-term sequelae; however, they should be observed for the cardiac signs of sudden β-blocker withdrawal.[245]

β-Adrenergic Receptor Blocker Withdrawal

After abrupt cessation of chronic β-blocker therapy, exacerbation of angina pectoris and, in some cases, acute MI and death have been reported.[84,246,247] Observations made in multiple double-blind randomized trials have confirmed the reality of a *propranolol withdrawal reaction*.[84,248] The mechanism for this reaction is unclear. There is some evidence that the withdrawal phenomenon may be due to the generation of additional β-adrenergic receptors during the period of β-blockade. When the β-blocker is then withdrawn, the increased β-adrenergic receptor population readily results in excessive β-adrenergic receptor stimulation, which is clinically important when the delivery and use of oxygen are finely balanced, as occurs in ischemic heart disease. Other suggested mechanisms for the withdrawal reaction include heightened platelet aggregability, an elevation in thyroid hormone activity, and an increase in circulating catecholamines.[84]

Similar withdrawal problems have been seen with β-blocker discontinuation in patients with heart failure previously responsive to treatment.[249,250]

Drug-Drug Interactions

β-Blockers are commonly used with other cardiovascular and noncardiovascular drugs, and the list of drugs with which they interact is extensive (Table 5–8).[229] The majority of the reported interactions have been associated with propranolol, the best studied β-blocker, and may not necessarily apply to other drugs in this class.

THROMBOSIS AND ISCHEMIC CARDIOVASCULAR DISEASE

The hemostatic process is a delicate balance of pro- and antithrombotic factors in the vasculature. Normal hemostasis prevents uncontrolled hemorrhage, however, these same

Table 5–8 Drug Interactions of β-Adrenergic-Blocking Agents

Cardiac Drugs	Interacting Drugs	Mechanism	Consequence	Prophylaxis
Hemodynamic Interactions				
All β-blockers	Calcium antagonists, especially nifedipine.	Added hypotension	Risk of myocardial ischemia	BP control, adjust doses
	Verapamil or diltiazem	Added negative inotropic effect	Risk of myocardial failure	Check for CHF, adjust doses
	Flecainide	Hypotension	Check LV function, flecainide levels	
	Sympathomimetics (S)	Opposing effects	Loss of clinical benefit	Avoid S
Electrophysiologic Interactions				
All β-blockers	Verapamil	Added inhibition of SA and AV nodes	Bradycardia, asystole, complete heart block	Exclude "sick sinus" syndrome, AV nodal disease; adjust dose; exclude prodrug LV failure
	Diltiazem	Added negative inotropic effect	Excess hypotension	
Hepatic Interaction				
Propranolol (P)	Cimetidine (C)	C decreases P metabolism	Excess P effects	Reduce both drug doses
	Lidocaine (L)	Low hepatic blood flow	Excess L effects	Reduce L dose
Metoprolol (M)	Verapamil (V)	V decreases M metabolism	Excess M effects	Reduce M dose
	Cimetidine (C)	C decreases M metabolism	Excess M effects	Reduce both drug doses
Labetalol (L)	Cimetidine (C)	C decreases L metabolism	Excess L and C effects	Reduce both drug doses
Carvedilol (CV)	Cimetidine (C)	C decreases CV metabolism	Excess CV effects	Reduce both drug doses
Antihypertensive Interactions				
All β-blockers	Indomethacin (I), other NSAIDs	I inhibits vasodilatory prostaglandins	Decreased antihypertensive effect	Omit I; use alternative drugs
Immune-Interacting Drugs				
Acebutolol	Other drugs altering immune status; procainamide, hydralazine, captopril	Theoretical risk of additive immune effects	Theoretical risk of lupus or neutropenia	Check antinuclear factors and neutrophils; low doses during cotherapy

AV, atrioventricular; BP, blood pressure; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; SA, sinoatrial.
From Frishman WH, Opie LH, Sica DA: Adverse cardiovascular drug interactions and complications. In Fuster V, Alexander RW, O'Rourke RA (eds): Hurst's The Heart, 11th ed. New York, McGraw-Hill, 2004, pp 2169-88.

pathways regulating hemostasis lead to pathological thrombosis and vessel occlusion. Distinct from venous thrombosis, arterial thrombosis is typically highly dependent on the platelet and vessel wall.[251] In the coronary artery, rupture of atheromatous plaque in variably stenosed vessels and subsequent thrombus formation underlies the majority of acute coronary syndromes. Vessel injury caused by plaque rupture exposes collagen and von Willebrand factor to platelets which adhere and further stimulate thrombus formation. Advances in understanding the mechanisms governing thrombosis have led to the development of new classes and combinations of antithrombotic drugs. Initially, characterization of arachidonic acid metabolism in platelets furthered an understanding of the therapeutic utility of cyclooxygenase inhibitors in vascular disease, most notably aspirin. The discovery and characterization of platelet receptors, such as the adenosine diphosphate (ADP) receptor and the glycoprotein IIb/IIIa complex (GP IIb/IIIa), have been associated with the development of novel classes of antiplatelet drugs, including thienopyridine derivatives and GP IIb/IIIa receptor antagonists.[251] Development of additional classes of antithrombin agents has also contributed to the ongoing changes in the guidelines for antithrombotic agents and the management of ischemic heart disease (Fig. 5–6; Table 5–9).

Platelet Inhibitors

Aspirin

Mechanisms of Action

Aspirin's primary antithrombotic effect is by inhibiting platelet aggregation via inactivation of cyclooxygenase (COX), a key enzyme in platelet arachidonate metabolism. More specifically, aspirin inhibits the cyclooxygenase (COX) activity of prostaglandin (PG) H-synthase, which in turn, blocks the metabolism of arachidonic acid to prostaglandin H_2 (PGH_2), the precursor of thromboxane (TXA_2) and other cyclic prostanoids (prostacyclin and other prostaglandins). In platelets, TXA_2 is synthesized and released in response to a variety of stimuli (i.e., collagen, adenosine diphosphate [ADP], thrombin, platelet activating factor) and acts to amplify the activation signal, promote irreversible platelet

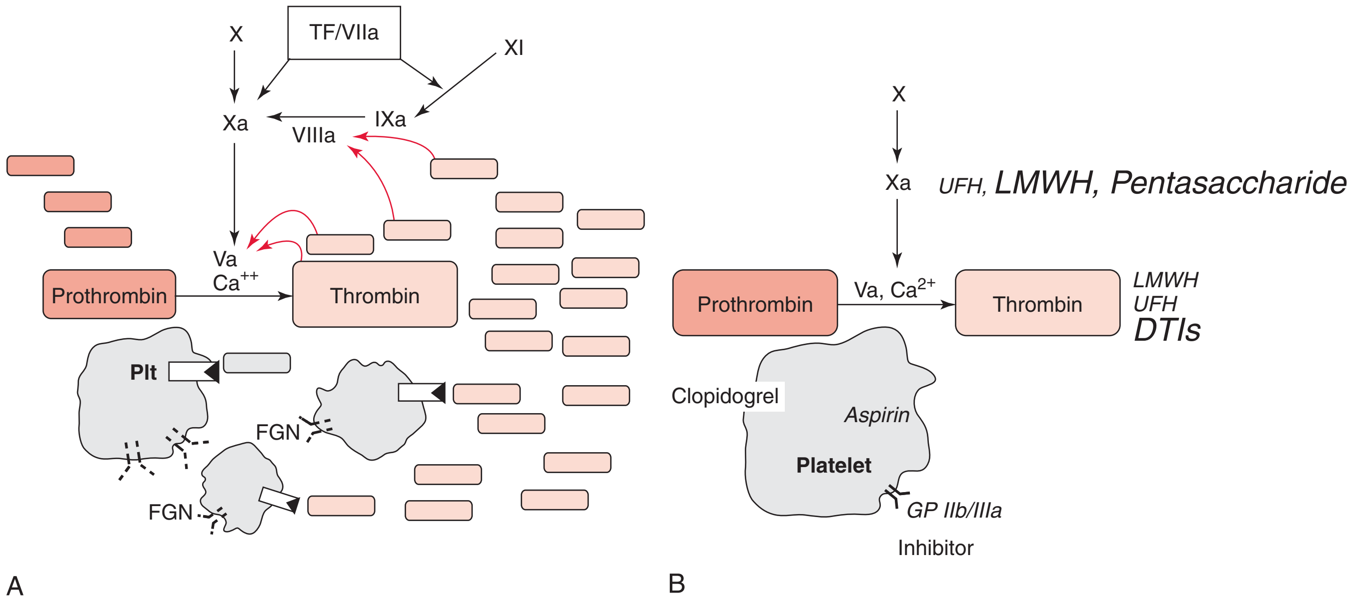


Figure 5–6 **Activated coagulation cascade and platelet aggregation in patients with an acute coronary syndrome. A,** With disruption of a vulnerable plaque, tissue factor (TF) is exposed and ultimately complexes with activated factor VII (VIIa). The TF:VIIa complex converts factor X to its active form (Xa) and triggers the coagulation cascade. Through a multiplier effect, a single molecule of factor Xa leads to downstream production of many molecules of thrombin through its participation in prothrombinase complex along with factor V and calcium (Ca^{++}) on a phospholipid surface, such as membrane of activated platelets (Plt). Following the initial triggering of the coagulation cascade, the process of thrombus formation is perpetuated by factors XI and IXa (intrinsic system). Thrombin amplifies the generation of factors VIIIa and Va that also perpetuates thrombus formation. Thrombin is a potent agonist for platelet activation via binding to thrombin receptor on platelets producing networking between the coagulation cascade and platelet activation. Aggregates of platelets are formed by cross-bridging via attachments of ligands such as fibrinogen (FGN) to the GP IIb/IIIa receptors on adjacent platelets. **B,** Sites of action of antithrombin and antiplatelet agents. Relative strength of actions at various positions is shown semiquantitatively by size of font in diagram. Thus, UFH has similar inhibitory action against thrombin and factor Xa; whereas LMWH has greater relative inhibitory capacity against factor Xa than thrombin. Direct thrombin inhibitors (DTIs) have little effect on generation of thrombin but are potent inhibitors of thrombin that has been formed. In contrast, the pentasaccharide acts more proximally in the coagulation cascade to inhibit formation of factor Xa and limit downstream production of thrombin. Combinations of antithrombins shown and antiplatelet agents (*bottom of diagram*) are effective in reducing the propensity to thrombus formation at the site of a disrupted vulnerable plaque. (Modified from: Antman EM: The search for replacements for unfractionated heparin. Circulation 2001;103:2311.)

aggregation, and cause vasoconstriction. Cyclooxygenase activity is inhibited by aspirin via the acetylation of a single serine residue at position 529 (Ser^{529}) within platelet PGH-synthase. There are two COX isoforms but COX-1 is primarily expressed in mature platelets.[252] Because platelets have minimal capacity for protein synthesis, the inactivation of COX-1 by aspirin is irreversible for the life of the platelet (8 to 10 days). The second COX isoform (COX-2) is inducible in newly formed platelets (8% to 10% of circulating platelets), and prostaglandin E_2 is the main product of platelet or endothelial COX-2 activity.[252] The concentration of newly formed platelets is large enough during periods of increased platelet turnover to produce detectable amounts of COX-2 derived TXA_2.

Aspirin may also influence hemostasis and cardiovascular disease by mechanisms independent of prostaglandin production. Although less clearly defined, the non–prostaglandin-mediated effects of aspirin on hemostasis are thought to be dose dependent and unrelated to COX-1 activity. These effects include vitamin K antagonism, decreased platelet production of thrombin, and acetylation of one or more clotting factors.[253] In addition to its direct platelet effects, aspirin may alter the pathogenesis of cardiovascular disease by protecting low density lipoprotein (LDL) from oxidative modification, improving endothelial dysfunction in atherosclerotic patients, and by attenuating the inflammatory response by acting as an antioxidant.[254]

Indication

Aspirin is an effective antiplatelet agent with proven benefit in the prevention of atherothrombotic complications of cardiovascular disease. Clinical trials have demonstrated that aspirin is effective for both the primary and secondary prevention of myocardial infarction, stroke, and cardiovascular death[255,256] and in the acute management of myocardial infarction, unstable angina, and embolic stroke (see Chapter 1).[256-258] A large, primary-prevention trial among women showed that aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes.[259] The results from this long-term trial also suggest that alternate day use of low-dose aspirin (100 mg) for an average 10 years of treatment does not lower total risk of, breast, colorectal, or other site-specific cancers.[260]

Despite proven benefit, the absolute risk of recurrent vascular events among patients taking aspirin remains relatively high, an estimated 8% to 18% after 2 years. Therapeutic resistance to aspirin might explain a portion of this risk[261] although the mechanism is uncertain. The answer is likely a combination of clinical, biologic, and genetic properties affecting platelet function, and the redundancy of platelet activation pathways and receptors may contribute to the problem of aspirin resistance.[261]

Dosages

Randomized trials have demonstrated that aspirin's therapeutic benefits are achieved from a variety of doses (30 to 1500 mg/d) but the optimal daily dose has not been unequivocally determined.[253,262] In general, higher dose regimens (500 to 1500 mg/d) are not associated with significant added benefit, might actually attenuate the antithrombotic effect of aspirin, and have been associated with increased risk of adverse effects.[253,262] Analyses of patients with acute coronary syndromes enrolled in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) IIb and Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials failed to demonstrate a significant difference in 6 month outcomes among patients taking low (<150 mg/d) and intermediate (≥150 mg/d) dose aspirin.[263] Based on earlier randomized trial protocols and clinical experience, the initial dose for the acute management of patients presenting with ACS should be between 162 and 325 mg.[264] Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with nonenteric formulations. Given the dose-related risks of bleeding, it is desirable to use a lower dose during the chronic phase of management of ischemic heart disease—typically, enteric-coated preparations of 75 to 162 mg are prescribed.[264]

Side Effects and Contraindications

Aspirin can cause minor bleeding but rarely causes major bleeding except in subjects with coagulopathies or in those who are being treated with other anticoagulants (i.e., warfarin).[264] Use of aspirin is associated with a small increase in the incidence of hemorrhagic stroke in healthy men, but in secondary prevention trials, aspirin reduces the overall

Table 5–9 Current Antithrombotic/Antiplatelet Recommendations from the AHA/ACC Guidelines for Unstable Angina/Non–ST-Segment Elevation MI

	Agent	Recommendation Level	Other
Antiplatelet agents	Aspirin	IA	
	Clopidogrel	IA	
	GP IIb/IIIa	Eptifibatide-IA Tirofiban-IA Abciximab-IA	Abciximab is not indicated (IIIA) without cardiac catheterization
Antithrombin agents	Heparin	IA	
	LMWH	Enoxaparin-IIA	Other LMWH not recommended

LMWH, low-molecular-weight heparin.
Adapted from Gibler WB, Cannon CP, Blomkalns AL, et al: Practical implementation of the guidelines for unstable angina/non–ST-segment elevation myocardial infarction in the emergency department: A scientific statement from the American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care), Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration with the Society of Chest Pain Centers. Circulation 2005;111:2699-710.

incidence of stroke. The side effects of aspirin are primarily gastrointestinal, dose related, and ameliorated by using low doses (75 to 162 mg per day). Aspirin use can also lead to gastric erosions, hemorrhage, and ulcers that can contribute to anemia.[264] Reinforcing these observations, a study combined 31 clinical trials to compare the risk of hemorrhage in the setting of low (<100 mg), moderate (100 to 200 mg), and high (>200 mg) doses of aspirin.[265] Low-dose aspirin was associated with the lowest risk, and moderate doses caused a relatively high hemorrhagic event rate—especially with regard to minor, gastrointestinal, total bleeding, and stroke.[265]

Aspirin Resistance

The concept of therapeutic aspirin resistance originated because the immediate biologic effects of aspirin are not uniform among all subjects. Variability in aspirin-mediated platelet inhibition has subsequently been documented among normal subjects, in patients with cerebrovascular disease, stable coronary artery disease, and in those presenting for coronary artery bypass surgery.[261] Despite the apparent consistency of these observations, the exact prevalence of aspirin resistance remains uncertain. The absence of standardized diagnostic criteria or a single validated method of identifying affected individuals has lead to a wide range of population estimates.[261] However, the fact that biochemical measures of aspirin nonresponsiveness have been documented in a wide range of patient populations does not necessarily mean that it has a causal association with cardiovascular disease.

Thienopyridines

Mechanisms of Action

The thienopyridine derivatives, ticlopidine and clopidogrel, are inhibitors of ADP-induced platelet aggregation. The antiplatelet effect of thienopyridine derivatives is due to irreversible inhibition of ADP binding to platelet purinergic receptors (Fig. 5–7).[266-268] Ticlopidine and clopidogrel are inactive in vitro and must be administered in vivo to exhibit antiaggregatory and antithrombotic activities. An active metabolite can be generated from human liver microsomes incubated with clopidogrel.[266] Metabolism of clopidogrel by the hepatic cytochrome P450 enzyme system to an active metabolite[266,267] is essential for its in vivo antiplatelet effects.[266,267] This metabolite of clopidogrel displays the same in vivo effects as seen in vitro, such as inhibition of adenylyl cyclase and inhibition of ADP-induced aggregation.[266,267] Both drugs are mechanistically and structurally similar; however, owing to a higher incidence of severe neutropenia and other adverse effects associated with ticlopidine, clopidogrel has become the primary thienopyridine derivative used in clinical settings.[269]

Indication

Over the past several years, the indications for clopidogrel in patients with ischemic heart disease continue to expand. The effects of a daily dose of clopidogrel (75 mg) have been compared with those of a daily dose of aspirin (325 mg) in individuals at risk for ischemic events. Long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death.[269] Both drugs were equally as effective in the prevention of vascular ischemic events in patients who had recently suffered from a myocardial infarction or ischemic stroke. In individuals who had symptomatic atherosclerotic peripheral arterial disease, however, clopidogrel was more effective than aspirin at reducing the incidence of vascular ischemic events. Adding clopidogrel to aspirin within the first 30 days and later (31 days to 12 months) in patients with acute myocardial infarction reduced the risk of ischemic vascular events with benefit emerging within 24 hours of initiation of treatment and continuing throughout the 12 months (mean 9 months) of the study.[270] The benefit of clopidogrel demonstrated in the CURE trial is consistent in low-, intermediate-, and high-risk patients with acute coronary syndromes (as stratified by TIMI risk score), thus supporting its use in patients with documented non–ST-segment elevation acute coronary syndromes.[271] In patients with acute coronary syndrome receiving aspirin, a strategy of a loading dose of clopidogrel followed by long-term maintenance therapy is beneficial in reducing major cardiovascular events, compared with placebo.[258] Clopidogrel has also been shown to be protective when used as an adjunct to fibrinolysis without a significant increase in major bleeding.[272]

With the success of clopidogrel, other thienopyridines are being developed. Prasugrel (CS-747, LY640315), a novel potent thienopyridine $P2Y_{12}$ receptor antagonist, has the potential to achieve higher levels of inhibition of ADP-induced platelet aggregation than currently approved doses of clopidogrel.[273] In a phase 2 study, when administered at the time of percutaneous coronary intervention, prasugrel and clopidogrel both resulted in low rates of bleeding.[274]

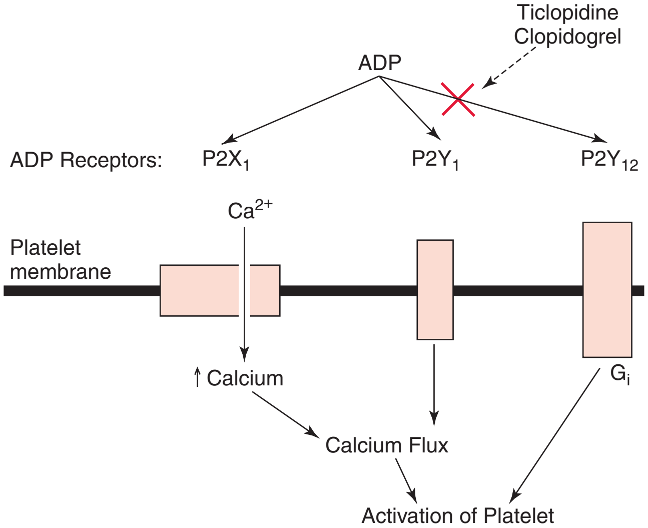


Figure 5–7 **Platelet activation by ADP.** Three receptors that can be activated by ADP are present in the platelet. These are G-protein–coupled receptors and they mediate different responses. The $P2Y_{12}$ receptor is the target for the antiplatelet thienopyridine derivatives, ticlopidine and clopidogrel.

Dosages

The standard dose of ticlopidine is 250 mg twice daily when used as an antithrombotic agent in patients with claudication, unstable angina, peripheral artery bypass surgery, and cere-

brovascular disease. Most studies of clopidogrel have used 300 mg immediately followed by 75 mg once daily.[256,270] As a result of the CURE trial, the FDA approved the 300 mg loading dose of clopidogrel because of the reduction in adverse cardiovascular events with dual antiplatelet therapy in acute coronary syndromes,[275] however, the precise loading dose and timing needed to achieve adequate anticoagulation continue to be areas of investigation. For low-to-intermediate risk patients treated with a 600-mg loading dose of clopidogrel before PCI, incremental clinical benefit within the first 30 days for pretreatment >2 to 3 hours was not evident.[276] It is unclear whether 600 mg results in additional and/or quicker antiplatelet effects because both the 300- and 600-mg loading doses appear to achieve the same degree of maximal platelet inhibition.[275] The safety of loading doses of clopidogrel greater than 600 mg also needs to be evaluated more rigorously before it can be recommended for routine use.[277]

Side Effects and Contraindications

Treatment with ticlopidine is associated with a high incidence of neutropenia (1%), which is usually reversible on discontinuation of treatment; however, in a few cases, it is irreversible and potentially fatal.[278] Patients must be periodically monitored, especially in the first 3 months of treatment, to detect this serious complication. Another potentially life-threatening complication of ticlopidine therapy is thrombotic thrombocytopenic purpura. Clopidogrel represents an advance in antiplatelet therapy because, compared with ticlopidine, its use is not complicated by neutropenia. It must be noted, however, that thrombotic thrombocytopenic purpura is still a harmful, albeit very rare, complication of clopidogrel treatment.[278]

The additional bleeding risk of thienopyridines appears to be dependent on the clinical setting. The risk of major bleeding has been shown to be increased among patients treated with clopidogrel.[256] Much of the debate centers around the increased bleeding noted among patients treated with clopidogrel who subsequently require surgery. In the CURE trial, the overall benefits of starting clopidogrel on admission appear to outweigh the risks, even among those who proceed to bypass surgery during the initial hospitalization.[257] However, it has been clearly shown that preoperative clopidogrel exposure increases the risk of reoperation and the requirements for blood and blood product transfusion during and after coronary bypass surgery.[279]

Current available data show that about 4% to 30% of patients treated with conventional doses of clopidogrel do not display an adequate antiplatelet response. The optimal level of clopidogrel-induced platelet inhibition, which will correlate quantitatively with clopidogrel's ability to prevent atherothrombotic events, is still not definitely known. In addition, because there is no validated platelet function assay to measure clopidogrel's antiplatelet effect, it is not justified to routinely measure clopidogrel resistance in the clinical setting.[280] The clinical implications of this variability are unknown but potentially are important. Future clinical trials may define whether hyporesponders to clopidogrel are at increased risk for thrombotic events and whether hyperresponders are at increased risk for bleeding. If these data become available, the individualization of antiplatelet therapy, including clopidogrel dosing, may be possible.[265]

Dipyridamole

Mechanisms of Action

Dipyridamole is a platelet inhibitor that is primarily recognized as an antithrombotic agent. In addition, through the generation of adenosine, dipyridamole evokes vasodilation and through the combination of these antiplatelet and vasodilator functions likely improves tissue perfusion. The European Stroke Prevention Study 2 (ESPS-2) demonstrated that treatment with dipyridamole was as effective as low-dose aspirin in the reduction of stroke risk.[281] Because dipyridamole is a weak direct platelet inhibitor, clinical observations such as this suggest that dipyridamole may have additional beneficial vascular effects. Dipyridamole has been reported to have antioxidant properties,[282] but the direct effect on vascular cells is not known. Dipyridamole is also a highly efficient chain-breaking antioxidant with fluorescence that is quantitatively quenched on reaction with peroxyl radicals.[282] Consistent with these observations, treatment with dipyridamole significantly limits ischemia-reperfusion injury in humans in vivo.[283]

Indication

Analysis using data from ESPS-2 has shown that, compared with aspirin alone, aspirin plus extended-release dipyridamole is efficacious in reducing the risk for stroke and vascular events among patients younger than 70 years; those with hypertension, prior stroke, or transient ischemic attack; current smokers; and those with any history of cardiovascular disease. Relative hazard reductions favored the combination of aspirin plus extended-release dipyridamole and were greatest for the high-risk patients.[284] Analysis of randomized controlled trials involving dipyridamole in patients with previous ischemic stroke or TIA showed that dipyridamole, given alone or with aspirin, reduces stroke recurrence in patients with previous ischemic cerebrovascular disease. The combination of aspirin and dipyridamole also reduces the composite of nonfatal stroke, nonfatal myocardial infarction, and vascular death when compared with aspirin alone.[285] However, most of these conclusions are based on a single trial and only in patients presenting after cerebral ischemia.

Dosages

A standard dose of dipyridamole is 200 mg plus acetylsalicylic acid 25 mg.[286] The first European Stroke Prevention Study (ESPS-1) which found the combination of aspirin/dipyridamole to be superior to placebo in the prevention of stroke and transient ischemic attack (TIA) evaluated dipyridamole 75 mg three times per day. The ESPS-1, however, did not include an aspirin-only treatment arm and, therefore, it was unclear whether the combination of aspirin/dipyridamole was superior to aspirin alone. As a result, a second trial was conducted that included treatment arms of aspirin alone, extended release dipyridamole alone, combination therapy, and placebo. The combination of aspirin 25 mg plus extended release dipyridamole 200 mg twice daily was shown in the ESPS-2 to be significantly better than either agent given individually in preventing stroke.[281]

Side Effects and Contraindications

Peak plasma concentrations are achieved after approximately 2 hours following oral administration of dipyridamole (200 mg

twice daily).[287] Although dipyridamole is highly lipophilic, it does not cross the blood-brain barrier to a significant degree. Dipyridamole is metabolized in the liver where it is conjugated and excreted through the bile into the feces.[287] Adverse events noted in ESPS-2 included mild gastrointestinal problems as well as infrequent serious bleeding.[281] The addition of dipyridamole to aspirin appeared to result in a bleeding risk similar to that of aspirin alone.[281] A contraindication for dipyridamole is for known hypersensitivity to the drug. As far more individuals have sensitivity to aspirin, care should be taken when giving Aggrenox, an aspirin/dipyridamole combination medication. Dipyridamole is excreted in breast milk and should be used with caution in nursing mothers.

Glycoprotein IIb/IIIa Receptor Antagonists

Mechanisms of Action

The GP IIb/IIIa receptor serves as a bidirectional conduit with GP IIb/IIIa-mediated signaling occurring immediately after the binding of fibrinogen and initiating intracellular signaling that further stabilizes the aggregate (Fig. 5–8). Calcium mobilization, tyrosine phosphorylation, activation of phosphoinositide metabolism, and cytoskeletal reorganization result from the activation of the GP IIb/IIIa complex. This series of events transforms platelet aggregation from a reversible to an irreversible process.

Although aspirin and clopidogrel are effective antiplatelet agents, they are relatively weak antiaggregatory drugs. Drugs that specifically target the GP IIb/IIIa receptor and prevent the binding of fibrinogen inhibit this final common pathway for platelet aggregation.[288] Platelet aggregation is completely inhibited by blockade of 80% of the surface GP IIb/IIIa receptors,[289] and antagonism of the GP IIb/IIIa receptor inhibits platelet aggregation, irrespective of the platelet activator. Multiple clinical trials have shown inhibition of GP IIb/IIIa to be a highly effective antithrombotic strategy.[290] There are several classes of GP IIb/IIIa inhibitors in clinical use. Abciximab is a Fab fragment of the 7E3 antibody that has high affinity and a slow rate of dissociation from GP IIb/IIIa. In contrast, the small molecules, eptifibatide and tirofiban, have a much more rapid rate of dissociation.

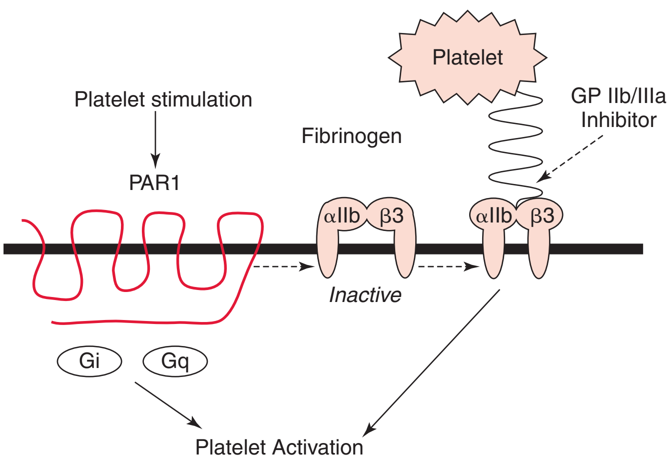


Figure 5–8 **Platelet aggregation and fibrinogen binding to glycoprotein IIb/IIIa.** Damage or vascular injury exposes subendothelial von Willebrand factor (VWF) or collagen to the circulating blood. Platelets adhere and events cause a conformational change in glycoprotein (GP) IIb/IIIa enabling the high affinity binding of fibrinogen which results in thrombus formation. This process can be attenuated by GP IIb/IIIa inhibitors.

Indications

Evidence supports the use of GP IIb/IIIa antagonists in patients with unstable angina/NSTEMI undergoing coronary intervention.[291-293] Current ACC/AHA Guideline Committee recommendations advise that high-risk patients, especially troponin-positive patients, should receive a GP IIb/IIIa antagonist. The small-molecule agents, eptifibatide and tirofiban, may be started 1 to 2 days before and continued during the procedure. Any of the GP IIb/IIIa antagonists may be started immediately before or during the procedure. None of the GP IIb/IIIa antagonists appears to be effective in the routine management of low-risk, troponin-negative patients in whom early coronary intervention is not planned.

The use of GP IIb/IIIa inhibitors in patients not undergoing coronary intervention is less clear. The small-molecule GP IIb/IIIa antagonists eptifibatide and tirofiban appear to modestly reduce the combined endpoint of death or myocardial infarction with some increase in bleeding.[294] As shown by a meta-analysis, the patients who underwent early revascularization appeared to derive the greatest benefit.[294] The use of abciximab in patients with UA/NSTEMI in whom intervention is not planned is not indicated based on the results of the GUSTO IV-ACS trial.[295]

Oral Glycoprotein IIb/IIIa Receptor Antagonists

Several ligands of integrins, including fibrinogen and von Willebrand factor, possess one of the two amino acid sequences 95-97 (Arg-Gly-Asp or RGD) and 572-575 (Arg-Gly-Asp-Ser or RGDS) that enable them to bind to the activated GP IIb/IIIa receptor and inhibit platelet aggregation.[296] These nonpeptide mimetics are unique in that they have the potential for oral administration that initially was thought to be useful for long-term antiplatelet therapy; however, several oral GP IIb/IIIa inhibitors have been evaluated, and their use has not been associated with clinical benefit.[297-300] Reasons for this discrepancy are unclear, and potential explanations have included hypothetical partial agonist activity, a prothrombotic effect of the oral compounds, or a direct toxic effect that is unrelated to platelet activation such as apoptosis.[301-303] Additionally, there has been the observation that some oral GP IIb/IIIa inhibitors augment small platelet microaggregate formation following stimulation.[302,303]

Dosages

The dose of GP IIb/IIIa antagonist depends on the specific agent being used. For abciximab, a bolus dose of 0.25 mg/kg followed by a 12-hour infusion at 0.125 μg/kg/min (to a maximum of 10 μg/min) with unfractionated heparin before the procedure is efficacious for patients undergoing coronary intervention.[304] For ongoing angina before intervention, a bolus of 0.25 mg/kg 18 to 24 hours before the procedure followed by a continuous infusion of 10 μg/min until 1 hour after the procedure (with heparin) has been used.[305]

Although lower doses have been used for percutaneous coronary interventions, eptifibatide is given as a double

bolus of 180 μg/kg (10 minutes apart) with an infusion of 2 μg/kg/min.[306] In unstable angina/NSTEMI, a 180 μg/kg bolus of eptifibatide is used followed by a 2 μg/kg/min infusion.[307] The infusion rate should be decreased by 50% in patients with a creatinine clearance of less than 50 mL/min.

Tirofiban is used as a bolus of 0.4 μg/kg/min over 30 minutes followed by an infusion of 0.1 μg/kg/min; it should be administered with heparin.[307] The infusion rate should be reduced by 50% in patients with a creatinine clearance of less than 30 mL/min.

Side Effects and Contraindications

The primary adverse reactions to GP IIb/IIIa receptor antagonists are bleeding and thrombocytopenia. Immune mechanisms responsible for the thrombocytopenia have been identified for all of the agents currently available in the United States. Although the overall incidence is relatively low, the effects may be life threatening. Thrombocytopenia with abciximab (as defined by a platelet count $<100 \times 10^9$/L) occurs in 2.5% to 6% of patients and severe thrombocytopenia (platelet count $<50 \times 10^9$/L) occurs in 0.4% to 1.6% of patients in reported clinical trials. Platelet transfusions were administered to 0.9% to 6% of patients in this setting.[290,308] Readministration of abciximab does not appear to have an enhanced risk when compared with primary exposure; however, the severity in those who develop thrombocytopenia may be greater.

Thrombocytopenia with eptifibatide is reported to occur between 1.2% and 6.8% of patients and platelet transfusions have been reported to be needed in 1.3% to 1.5% of patients.[306,309] Thrombocytopenia with tirofiban is reported to occur in 1.1% to 1.9% of patients with severe thrombocytopenia occurring in 0.2% to 0.5%.[307] It is important to note that treatment with these agents can also cause pseudothrombocytopenia, which occurs as a result of artifactual platelet clumping in vitro, yielding a falsely decreased platelet count. This observation may be dependent on the use of specific anticoagulants for the assays including citrate, ethylenediaminetetraacetic acid (EDTA), or nonchelating anticoagulants. The incidence of pseudothrombocytopenia may be as high as 2.1% with the use of abciximab. A smear to directly examine for the presence of clumped platelets may be required.

Thrombin Inhibitors

The standard antithrombotic agents are unfractionated heparin (and now low-molecular-weight heparin, LMWH) and warfarin. Owing to the limitations of these drugs, the evolution of antithrombotic treatment for cardiovascular disease has continued with the emerging importance of therapies focused on improved dosing and decreased laboratory monitoring, as well as enhanced efficacy and safety profiles. New antithrombotic strategies continue to evolve in three general directions. The best studied approach has been the development of direct inhibitors of specific coagulation factors. Direct inhibitors of thrombin (i.e., factor IIa) and factor Xa, two serine proteases with central roles in the coagulation cascade, have undergone clinical trials to define their role as adjuncts to thrombolysis and their use in preventing thrombosis after interventional cardiovascular procedures.

A second approach has been the production of recombinant endogenous anticoagulants including recombinant thrombomodulin. This also involves recombinant forms of antithrombin III and heparin cofactor II, which are serine protease inhibitors that interact with the glycosaminoglycan cofactors, heparin, heparan sulfate, and dermatan sulfate to inhibit coagulation factors. Another strategy is manipulation or synthetic production of endogenous, natural anticoagulant cofactors. This includes modification of native glycosaminoglycans, such as heparan sulfate, dermatan sulfate, or the heparin pentasaccharide, to enhance their anticoagulant activity.

Unfractionated Heparin

Mechanisms of Action

Almost all heparin preparations are extracted from porcine intestinal mucosa or bovine lung and consist of both high-molecular-weight and low-molecular-weight fractions. The high-molecular-weight fraction (average molecular mass, 20 kD) comprises 66% of a given preparation by mass, has a weak anticoagulant effect, and can activate platelets. The low-molecular-weight fraction (average molecular mass, 7 kD) represents approximately 33% of a given preparation, possesses 85% of the total anticoagulant activity of the original sample, and causes little platelet activation. The low-molecular-weight and high-molecular-weight fractions are each characterized by subspecies with low and high affinities for antithrombin III. The heparin species with high affinity for antithrombin III possesses a critical pentasaccharide sequence that mediates this interaction. The low-molecular-weight heparin fraction with high affinity for antithrombin III represents that fraction with the most potent anticoagulant activity and the least platelet-stimulating activity.

Indications

Unfractionated heparin has been used in the management of unstable angina/NSTEMI for many years, and its benefit when added to aspirin has been clearly established.[291] In addition, many of the platelet inhibitor trials have been conducted with the coadministration of heparin. This has established heparin as a class IA therapy when used with platelet inhibitors.

The use of heparin as an adjuvant with fibrinolysis has also been examined in clinical trials. The use of subcutaneous or intravenous heparin as an adjunct to streptokinase remains controversial. Heparin is, however, recommended in streptokinase-treated patients who are at high risk of thrombosis.[310] Patients with STEMI who are receiving tPA should also be given heparin (as a 60 U/kg IV bolus maximum 4000 U at the time of initiating the tPA infusion, with an initial maintenance infusion of 12 U/kg/hr at a maximum of 1000 U/hr to maintain the aPTT at 1.5 to 2 times the control rate).[310] A 48-hour infusion is likely to be sufficient if aspirin is being given, and IV heparin therapy should be sustained only if there appears to be a high risk of systemic embolism such as a large anterior MI, CHF, previous systemic embolus, or atrial fibrillation. Otherwise, only low-dose heparin therapy (7500 U SC every 12 hours) is indicated as temporary prophylaxis against venous thrombosis. It has been suggested that a similar approach may be used for patients who have received reteplase or tenecteplase (TNK).[310]

Dosages

Heparin is cleared through a combination of a rapid saturable mechanism and a much slower mechanism with first-order mechanics. The slower, unsaturable mechanism of clearance is largely renal. These kinetics make the anticoagulant response to heparin nonlinear at therapeutic doses, with both the intensity and duration of effect rising disproportionately with increasing dose. Thus, the apparent biological half-life of heparin increases from 30 minutes after an IV bolus of 25 U/kg to 60 minutes with an IV bolus of 100 U/kg and 150 minutes with a bolus of 400 U/kg.[311-313] In patients with unstable angina, the dose of heparin is usually adjusted to maintain aPTT at an intensity equivalent to a heparin level of 0.2 to 0.4 U/mL as measured by protamine titration or by an anti-factor Xa level of 0.30 to 0.7 U/mL. For many aPTT reagents, this is equivalent to a ratio (patient/control aPTT) of 1.5 to 2.5.[311-313] As noted, heparin is normally administered with an initial 60 U/kg (maximum 4000 U) IV bolus, followed by IV infusion of 12 U/kg/hr (maximum 1000 U/hr), adjusted to maintain the aPTT at 1.5 to 2.0 times the control value. Treatment is usually initiated within 24 hours after the onset of chest pain.[311-313]

Side Effects and Contraindications

The primary side effect associated with the use of unfractionated heparin is bleeding. The risk of bleeding with IV unfractionated heparin is <3% in recent trials.[314] This bleeding risk increases with higher heparin dosages, concomitant use of antiplatelet drugs or oral anticoagulants, and increasing age (>70 years).[314]

Another problem associated with heparin is the development of heparin-induced thrombocytopenia (HIT), usually developing between 5 and 15 days after the initiation of heparin therapy. A more rapid onset form may occur in patients who have previously been exposed to heparin. HIT occurs when heparin binds to platelets, leading to platelet activation and the release of platelet factor 4. Antibodies are generated against the heparin/platelet factor 4 complex. The thrombosis associated with this syndrome may be due to immune-mediated platelet activation and microparticle formation. In the setting of HIT, an alternative antithrombin drug must be selected, and several have been approved by the FDA specifically for this use. Less commonly, long-term use of heparin is also associated with the development of osteoporosis and rare allergic reactions.

Low-Molecular-Weight Heparin

Mechanisms of Action

The use of unfractionated heparin has several limitations that include nonspecific binding, the production of antiheparin antibodies that may induce thrombocytopenia, continuous intravenous infusion, and the need for frequent monitoring. Because of the many known limitations associated with the use of unfractionated heparin, LMWHs have been developed. Issues such as continuous IV infusion and frequent monitoring are not problems normally encountered with the use of LMWHs. LMWHs are potent inhibitors of both thrombin (anti-IIa effects) and factor Xa. LMWHs can be given by subcutaneous administration and have a rapid and predictable absorption. The LMWHs also produce fewer platelet agonist effects and are less often associated with heparin-induced thrombocytopenia. These advantages have been well demonstrated in patients with venous disease and are now emerging for those with unstable angina.[310]

Indications

LMWHs have been studied in the treatment of ST-elevation myocardial infarction (STEMI) and in patients receiving fibrinolysis. Although the data have been mixed, in a number of trials evaluating its use in STEMI, LMWH has been found to have improved efficacy as compared with unfractionated heparin. A meta-analysis from the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and the Thrombolysis in Myocardial Infarction (TIMI) 11B studies has shown that enoxaparin is superior to unfractionated heparin in reducing the composite endpoints of death, myocardial infarction, and emergency revascularization in patients with Q-wave myocardial infarction.[315,316] A subsequent meta-analysis by Petersen and coworkers that pooled the data from six trials of enoxaparin in non–ST-segment elevation ACS showed significant reductions in death/MI by 30 days, especially in patients who had not received any antithrombin before randomization.[317] In contrast, the observations with other LMWHs, including dalteparin and fraxiparine, have been less encouraging. This may be due to enoxaparin's greater anti-Xa-to-anti-IIa ratio when compared with dalteparin, the greater severity of illness in the patients enrolled in the reported studies, and the extension of its antithrombotic actions to include inhibition of platelet aggregation by suppression of the release of von Willebrand factor.[318] The ACC/AHA guidelines suggest that enoxaparin, but not the other LMWHs, is preferred over unfractionated heparin for the medical management of UA/NSTEMI unless coronary artery bypass grafting (CABG) surgery is planned within 24 hours (Class IIa recommendation). Patients with elevated troponin values may derive the greatest benefit.

The current ACC/AHA guidelines also state that it is reasonable (Class IIb) to consider a LMWH as an alternative to unfractionated heparin in patients receiving fibrinolytic therapy who are <75 years of age and free of renal dysfunction.[292] Clinical trials have also demonstrated similar safety with LMWHs when compared with unfractionated heparin in the setting of PCI and in conjunction with glycoprotein IIb/IIIa inhibitors. Further study is needed to define the benefit of LMWHs in relevant high-risk subgroups before their use can be universally recommended (see Chapter 11 for further discussion).[319]

Dosages

In the setting of fibrinolysis, enoxaparin is given as a 30-mg intravenous bolus before fibrinolytic administration. Enoxaparin at a dose of 1 mg/kg subcutaneously is given twice daily for 48 hours.[320,321] The dosing regimen should be changed to 1.0 mg/kg subcutaneously every 24 hours for patients with an estimated creatinine clearance of <30 mL/min. Typically, the enoxaparin regimen is maintained for the duration of the hospitalization or day 8, whichever comes first. Continuing therapy after discharge has not shown benefit.[320,321]

In the setting of PCI, enoxaparin has been administered in several ways.[320,321] The first dosing regimen option is 1 mg/kg subcutaneously twice daily. When this route is used, it is important to ensure that the last dose of subcutaneous LMWH is administered within 8 hours of the procedure and that at least 2 subcutaneous doses of LMWH are given before

the procedure to ensure steady state. The second dosing regimen option is 1 mg/kg subcutaneously twice daily plus 30 mg intravenously at the time of PCI. This regimen can be used if >8 hours has passed since the last subcutaneous dose of enoxaparin. The third dosing regimen option is 1 mg/kg enoxaparin intravenously (if no GP IIb/IIIa inhibitor is used) or 0.75 mg/kg (if a GP IIb/IIIa inhibitor is used) at the time of PCI.[320,321] For elective PCI, an intravenous dose of 0.5 mg/kg was found to be safe in the STEEPLE study.[321a]

Side Effects and Contraindications

As with unfractionated heparin, LMWH should not be given to patients with contraindications to anticoagulant therapy such as active bleeding, significant thrombocytopenia, recent neurosurgery, intracranial bleed, or ocular surgery. Caution should be exercised in patients with bleeding diathesis, brain metastases, recent major trauma, endocarditis, and severe hypertension. LMWH is associated with less major bleeding compared with UFH in acute venous thromboembolism. UFH and LMWH are not associated with an increase in major bleeding in ischemic coronary syndromes, but are associated with an increase in major bleeding in ischemic stroke.[314] Patients treated with LMWH can develop HIT, and these drugs are not recommended for use in patients with documented or suspected HIT. Patients with renal dysfunction (usually defined as serum creatinine level >2 [in men] or 2.5 [in women] mg/dL) have been excluded from major studies of enoxaparin. Appropriate dosing in obese patients is unclear and is a current area of investigation.

Direct Thrombin Inhibitors

Direct thrombin inhibitors block thrombin's substrate interactions and inactivate fibrin-bound thrombin and fluid-phase thrombin. Direct thrombin inhibitors do not bind to plasma proteins or to platelet factor 4.[322]

Hirudin (lepirudin)

Mechanisms of Action

Hirudin is a polypeptide found in the salivary glands of the leech *Hirudo medicinalis,* and it is among the most potent of the natural thrombin inhibitors. Various biochemical and molecular biological techniques have been used to study the specific nature of the hirudin-thrombin interaction. The aminoterminal region of hirudin binds via hydrophobic interaction with the apolar binding site of thrombin. The carboxyterminal region appears to bind ionically to the anion binding exosite of thrombin. Direct interaction of hirudin with both the catalytic site and the anion binding exosite of thrombin probably accounts for its potent inhibition of all thrombin-mediated reactions, and this inhibition is equipotent toward free and fibrin-bound thrombin. The most commonly used measures for the anticoagulant activity of hirudin are the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Hirudin does not have direct effects on platelet aggregation or secretion, and the bleeding time is not altered significantly.

Indications and Dosages

Both the TIMI-9 and the Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO) II trials compared a single dose of heparin with a single dose of hirudin.[323] Both trials initially used high doses of hirudin (0.6 mg/kg bolus followed by 0.2 mg/kg/hr) and weight-adjusted heparin, and both trials were terminated prematurely because of an unacceptably high rate of intracerebral hemorrhage in both treatment arms. These trials were continued as TIMI-9b and GUSTO IIb, using lower doses of both hirudin (0.1 mg/kg bolus followed by 0.1 mg/kg/hr) and heparin (not weight adjusted). Results from the TIMI-9b trial showed heparin and hirudin to be equally effective as adjunctive therapies for streptokinase or t-PA in individuals with acute Q-wave myocardial infarction, without a difference in bleeding events.[324] Results of the GUSTO IIb trial[325] showed a marginally significant benefit of hirudin over heparin early after infarction in individuals with both Q wave and non–Q-wave myocardial infarction; however, this effect lessened over time.

Results from the Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) trial suggest that recombinant hirudin may be useful when compared with heparin in preventing cardiovascular death, myocardial infarction, and refractory angina with an acceptable safety profile in patients who have unstable angina or acute myocardial infarction without ST elevation and who receive aspirin.[326] In this study, 10,141 patients with unstable angina or acute myocardial infarction without ST elevation were randomly assigned heparin (5000 units bolus then 15 U/kg/hr; n = 5058) or hirudin (0.4 mg/kg bolus then 0.15 mg/kg/hr infusion; n = 5083) for 72 hours. At 7 days, 213 (4.2%) patients in the heparin group and 182 (3.6%) in the hirudin group had experienced cardiovascular death or new myocardial infarction (relative risk 0.84 [95% CI 0.69 to 1.02]; P = 0.077).[326]

An approved clinical application for recombinant hirudin (lepirudin) is in the treatment of HIT. When compared with historical controls, lepirudin-treated patients had consistently lower incidences of combined endpoints primarily because of a reduced risk for new thromboembolic complications. During treatment with lepirudin, aPTT ratios of 1.5:2.5 produce optimal clinical efficacy with a moderate risk for bleeding, aPTT ratios lower than 1.5 are subtherapeutic, and aPTT levels greater than 2.5 are associated with high bleeding risk. Bleeding events that require transfusion were significantly more frequent in patients taking lepirudin than in historical control patients. Lepirudin has also been used for anticoagulation in patients treated with extracorporeal circulation during open heart surgery. Comprehensive data on this group of patients, however, are lacking.

Dosages

Hirudin is used in the dosages discussed earlier. It has a narrow therapeutic window and requires monitoring, particularly when it is administered with thrombolytic agents. It is often given as a 0.4 mg/kg bolus, followed by a 0.15 mg/kg/hr infusion for 72 hours to maintain the aPTT between 60 and 100 seconds.

Side Effects and Contraindications

Hirudin should not be used in settings where anticoagulation is contraindicated. The risk of bleeding with hirudin is increased in the setting of concomitant anticoagulation or platelet inhibitors. Hirudin is renally cleared and should not be used in patients with renal dysfunction.

Argatroban

Mechanisms of Action

Another potent direct thrombin inhibitor is (*2R,4R*) 4-methyl-[N^{2-}(3-methyl-1,2,3,4-tetrahydro-8-quinolinyl) sulfonyl]-2-piperidine carboxylic acid, or argatroban. This compound is a synthetic N^2-substituted arginine derivative that binds to the catalytic site of thrombin with high affinity. It binds rapidly and reversibly to both clot-bound and soluble thrombin. Argatroban has a relatively short elimination half-life (39 to 51 minutes) and its reversible binding allows for rapid restoration of normal hemostasis on cessation of therapy. Argatroban has a predictable dose response that correlates with changes in anticoagulant parameters.

Indications

Studies with argatroban primarily have assessed its use as adjunctive therapy with fibrinolytics, in the treatment of HIT, or in patients undergoing coronary angioplasty. Data with argatroban are limited and it is approved only for use in HIT. Argatroban causes a dose-dependent increase in aPTT and TT. The half-life of the anticoagulant effect is approximately 25 minutes when argatroban is used alone.

For patients with HIT who are administered intravenous argatroban, benefit is noted as compared with historical controls. In HIT patients, argatroban therapy, compared with historical controls, improves outcomes, particularly new thrombosis and death caused by thrombosis.[327]

Dosages

In individuals with unstable angina, argatroban (0.5 to 5.0 μg/kg/min for 4 hours) is administered. For patients with HIT, argatroban, 2 μg/kg/min, is adjusted to maintain the activated partial thromboplastin time at 1.5 to 3 times the baseline value for a mean of 5 to 7 days.

Side Effects and Contraindications

Patients who have contraindications to anticoagulant therapy, as previously discussed, should avoid using argatroban. Argatroban is metabolized by the liver. In patients with hepatic impairment, the maximum concentration and half-life of argatroban are increased approximately two- to three-fold and clearance is one fourth that of healthy volunteers.

Bivalirudin (Hirulog)

Mechanisms of Action

Hirudin-derived thrombin inhibitors known as hirulogs are synthetic peptides that contain the two distinct domains of hirudin with antithrombin activity. Hirulog-1 (bivalirudin) contains a thrombin active-site inhibitory fragment, D-Phe-Pro-Arg-Pro, and a thrombin anion binding exosite recognition sequence that is analogous to hirugen. These fragments are joined by a glycine spacer at least four residues in length. Subtle modifications of hirulogs can increase their affinity for thrombin to a level equal to that of native hirudin.

Indications

Bivalirudin has been investigated in STEMI with streptokinase but was associated with excess bleeding. In individuals undergoing coronary angioplasty, bivalirudin was efficient in preventing abrupt closure and was found to be safe. In addition, among individuals undergoing percutaneous transluminal coronary angioplasty for unstable or post-infarction angina, bivalirudin was as effective as heparin but was associated with lower rates of moderate bleeding. Although bivalirudin reduces ischemic complications and bleeding after PCI, further trials are needed to evaluate bivalirudin versus heparin in conjunction with clopidogrel, GP IIb/IIIa inhibitors, and current standards of coronary intervention.[328] The current recommended dose of bivalirudin in the setting of PCI is an intravenous bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/hr for the duration of the procedure. Five minutes after the bolus, an ACT should be measured and an additional 0.3 mg/kg given intravenously as needed. The infusion may be continued for 4 hours after the procedure at the discretion of the operator.

Oral Anticoagulants

Warfarin

Mechanisms of Action

Warfarin and coumarin derivatives are vitamin K antagonists that prevent the cyclic interconversion of vitamin K and its 2,3-epoxide. Vitamin K is a cofactor for posttranslational carboxylation of glutamic acid residues that are on the amino terminus of vitamin K-dependent coagulation factors including factors II, VII, IX, and X, and anticoagulant proteins (proteins C and S). The antithrombotic properties of coumarin derivatives are delayed for 72 to 96 hours.

Indications

Although standard for the treatment and prevention of venous thrombosis, oral anticoagulant therapy has also been investigated in patients with ischemic heart disease. Warfarin, in combination with aspirin or given alone, was superior to aspirin alone in reducing the incidence of composite events after an acute myocardial infarction but was associated with a higher risk of bleeding.[329] In this study (WARIS II), the combination therapy targeted an international normalized ratio (INR) of 2–2.5 and the warfarin alone group had a target INR of 2.8–4.2.

Using a fixed, low dose of warfarin added to aspirin in the long term after myocardial infarction did not demonstrate reduction in the combined risk of cardiovascular death, reinfarction, or stroke. A fixed, low dose of warfarin added to aspirin reduced the risk of stroke, but this was a secondary endpoint. The combination of aspirin and warfarin was also associated with an increased risk of bleeding.[330]

Although the studies have been mixed, current available data based on nearly 20,000 patients participating in randomized clinical trials demonstrate that, when given in adequate doses, oral anticoagulants reduce the rates of reinfarction and thromboembolic stroke—but they do so at the cost of increased rates of hemorrhagic events.[331] However, the use of warfarin, even in controlled trials, is fraught with difficulties, as in the WARIS II study, wherein the international normalized ratio (INR) was below target in about one third of patients, and those over 75 years of age were excluded.[331]

Dosages

Dosages of warfarin should be adjusted based on the INR, which in turn is based on the use of an International

Sensitivity Index (ISI) assigned to each thromboplastin reagent so as to standardize the dose.

Side Effects and Contraindications

Oral anticoagulants have a narrow therapeutic window and a highly variable dose-response relation. The most frequent complication of warfarin therapy is the risk of bleeding. The major determinants of vitamin K antagonist-induced bleeding are the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy. There is good evidence that vitamin K antagonist therapy with a targeted INR of 2.5 (range, 2.0 to 3.0) is associated with a lower risk of bleeding than is therapy targeted at an INR >3.0.[314]

A rare complication of warfarin therapy is skin necrosis. Warfarin-induced skin necrosis usually develops soon after initiation of therapy and is higher in frequency in patients with protein C or protein S deficiency. Patients with known protein C or S deficiencies should be started on warfarin only after therapeutic doses of heparin have been initiated. Warfarin is also teratogenic and its use should be avoided during pregnancy, although the use of oral anticoagulants versus heparin/LMWH during pregnancy is an ongoing area of investigation.

Oral Thrombin Inhibitors

Warfarin has limitations that are well established and include a narrow therapeutic index, the need for high quality dose management, and interactions with other drugs, foods, and comorbid conditions. In the interest of developing safer and more effective oral anticoagulants, orally active direct inhibitors of thrombin are being investigated with the hopes of replacing the coumarins for the long-term treatment of thromboembolic disorders. Important issues in the profile of the ideal thrombin inhibitor include safety, potency, selectivity, oral bioavailability, and half-life. The furthest along in development has been ximelagatran, an agent that was thought to be promising owing to its rabid absorption, low protein binding, lack of drug interactions, and fixed dose. However, ximelagatran failed to receive FDA approval because of the potential for hepatotoxicity. Other oral thrombin inhibitors are undergoing clinical study.

Fibrinolytics

Fibrinolytic drugs have been incorporated into the standard management of ST-segment elevation myocardial infarction. With these therapies, short-term mortality gains are accompanied by an improvement in ventricular function and a reduction in major cardiovascular complications. Follow-up studies have demonstrated that these short-term gains, after a single fibrinolytic administration, are sustained for at least 8 years. Of note, only about 50% of patients achieve normal epicardial coronary artery flow (TIMI 3) within 90 minutes of administration of tPA or TNK.

Mechanisms of Action

Plasminogen is a proenzyme that is converted to the active enzyme plasmin by plasminogen activators. Plasmin degrades fibrin into soluble degradation products. Plasminogen activators cause thrombus dissolution by initiating this cascade. This process is inhibited by plasminogen activator inhibitors that prevent excessive plasminogen activation by t-PA and urokinase-type plasminogen activator (uPA).

Indications

Fibrinolytic therapy has been used in patients who have had at least 30 minutes of ischemic chest pain and either 1 mm of ST-segment elevation in at least two adjacent limb leads, 2-mm ST-segment elevation in at least two adjacent precordial leads, or complete bundle branch block.[332] Patients should be treated within 12 hours of the onset of symptoms. Most important in terms of survival advantage is the time from the onset of symptoms to the initiation of therapy. There does not appear to be benefit when fibrinolytic therapy is used for unstable coronary syndromes not associated with ST-segment elevation.[333]

Dosages

Streptokinase is usually administered as an intravenous infusion of 1.5 million units over 30 to 60 minutes. Recombinant tissue plasminogen activator is relatively fibrin selective. The most commonly used dose of tPA is administered as a 15 mg bolus over 3 minutes, followed by a 0.75 mg/kg (not to exceed 50 mg) over 30 minutes, and then 0.5 mg/kg (not to exceed 35 mg/kg) over an additional 60 minutes.

Reteplase is a truncated form of tPA that lacks the first Kringle domain. It has a longer half-life as compared with tPA but has not shown superiority over accelerated tPA. It is administered as two intravenous boluses of 10 U given 30 minutes apart with each bolus administered over 2 minutes.

Tenecteplase is a mutated form of tPA that has an extended half-life and greater fibrin specificity. It is equivalent to accelerated tPA and can be given in a single bolus (5 to 10 seconds) in a dose according to body weight: 30 mg to patients who weigh less than 60 kg; 35 mg to those who weigh 60 to 69.9 kg; 40 mg to those who weigh 70.0 to 79.9 kg; 45 mg to patients who weigh 80.0 to 89.9 kg; and 50 mg to patients who weigh 90.0 kg or more.[334]

Side Effects and Contraindications

Bleeding is the major adverse side effect common to fibrinolytic agents. The risk of intracranial hemorrhage averages 0.5% with the relatively fibrin-specific agents; rates of ICH rise to 1% to 2% with increasing patient age. Streptokinase is known to have allergic reactions in approximately 5% of patients, but anaphylaxis is rate.

THROMBOSIS: FUTURE DIRECTIONS

An important lesson that has emerged from the numerous trials aimed at treating acute cardiovascular thrombosis is that increased antithrombotic potency may not guarantee enhanced clinical benefit. It is not known whether this is due to problems with the specific antithrombotic agents, the risk of bleeding, or the inherent limitations of our current means of measuring thrombosis. Novel therapies are also being developed to target alternative and redundant thrombotic pathways including (Table 5–10) new inhibitors of the $P2Y_1$ and $P2Y_{12}$ receptors,[335] the CD40-CD40 ligand system, adhesion molecules, CD39/ATPDase, and the GPIb-V-IX complex–von Willebrand factor.[336] New anticoagulants are being developed that will also address some of the limitations

Table 5–10 Platelet Inhibitors Under Development and Their Mechanism of Action

Therapeutic Agent	Mechanism of Action	
Nitroaspirin (NCX4016)	NO donor[338]	
P2Y12 antagonist (AR-C69931 MX)	Purinergic receptor inhibitor[335]	
VWF-GPIb-IX inhibitors	Inhibit platelet adhesion	
Collagen-GPVI inhibitors	Inhibit platelet adhesion	Inhibit aggregation
Thrombin-platelet inhibitors	Inhibit PAR-1 receptors	Inhibit PAR-4

of the currently available drugs.[1] Direct inhibitors targeting the initiation of coagulation have been studied and include active-site blocked factor VIIa and tissue factor pathway inhibitors. In addition, inhibitors of the propagation of coagulation are being examined including Factor IXa inhibitors, direct and indirect Factor Xa inhibitors (oral and intravenous), and modulators of the protein C pathway. However, with all of these agents, it is not yet clear whether the new target and/or ease of use can overcome noted side effects including toxicity, bleeding, and contact system activation (See Chapters 10 and 11 for further discussion).[339]

Continued studies will refine the implementation of current therapy; target therapy given selectively to high-risk patients and to those likely to respond (pharmacogenomics); and study the incremental benefits and safety of various antiplatelet combinations and their interactions with other medications.[251] Continuing advances in understanding the mechanisms of thrombosis, as well as the development of new techniques for studying its regulation, have led to an enhanced understanding of thrombotic disease as well as to the availability of new classes of antithrombotic drugs.

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Chapter 6

Mechanical Approaches to Percutaneous Coronary Intervention

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CHAPTER CONTENTS

Interventional cardiology, the application of catheter-based techniques to the treatment of coronary artery, valvular, or congenital cardiac diseases, arose as the culmination of the use of catheters as instruments for the *diagnosis* of heart disease. Cournand[1] and others first reported on the potential utility of the right heart catheter in 1941, leading ultimately to the development in the late 1950s and 1960s of selective coronary arteriography by Sones and Judkins. Dotter and Judkins introduced the therapeutic application of percutaneous angioplasty of atherosclerotic peripheral vascular stenoses in 1964 with a cumbersome system of multiple coaxial catheters.[2] The modern era of cardiovascular intervention began with the development by Andreas Gruentzig of a balloon catheter, with which the first percutaneous transluminal coronary angioplasty (PTCA) procedure was performed in 1977 in Zurich.

Since the 1970s, there has been explosive growth in the field of interventional cardiology. Although this technique was initially restricted to relatively young patients with stable angina, normal left ventricular function, and simple stenoses of a single coronary artery, current indications have expanded to include unstable angina and acute myocardial infarction, elderly patients and those with depressed left ventricular function, multivessel coronary artery disease, and stenoses with complex morphology or in coronary artery bypass grafts. A variety of devices for coronary intervention have been advocated to overcome some of the limitations of balloon angioplasty in treating lesions with high-risk characteristics or reversing the complications of balloon dilation. Stents were developed and shown to reduce the incidence of vessel closure and restenosis after balloon angioplasty. To further address the problems of in-stent restenosis, drug-eluting stents (stents coated with anti-proliferative medications) were designed. Imaging techniques including intravascular ultrasound and Doppler flow assessment provide information regarding plaque morphology and physiological function which are complementary to data derived from conventional contrast angiography, facilitating the selection of optimal means of revascularization and assessment of outcome.

CORONARY ANGIOPLASTY

Since the introduction of coronary balloon angioplasty into clinical practice in 1977,[3] improvements in equipment design and operator experience have permitted this procedure to be applied to the treatment of a broad spectrum of coronary artery disease. The development of new devices for percutaneous coronary revascularization was motivated by the recognition that, despite improvements in equipment design and operator experience, balloon angioplasty remained substantially limited by the risk of procedural complications, by difficulties in achieving an adequate angiographic result, and, most importantly, by the persistently high incidence of restenosis. Stenoses that are complex, calcified, long, bulky, eccentric, totally occluded, within saphenous vein grafts, or that are associated with thrombus are particularly challenging to treat with conventional methods of balloon dilation. The potential efficacy of new devices relative to PTCA appears to be twofold. First, the mechanical support of the arterial wall afforded by stents reduces acute ischemic complications caused by vascular disruption and later restenosis caused by recoil and remodeling. Second, in certain high-risk lesion subsets, other devices can achieve a better angiographic result—for instance, by actual removal of plaque.

Equipment

Guide catheters of diameters ranging from 5 to 9 Fr provide atraumatic coronary ostial engagement and support for passage of dilation catheters with profiles of 0.9 mm (distal external diameter). Steerable guidewires, with diameters of only 0.009 to 0.018 inches and tips of varying degrees of stiffness, can be precisely shaped allowing even distal coronary lesions beyond tortuosity to be routinely accessed. Current balloon angioplasty catheters have deflated profiles of 1 mm or less and shaft constructions that optimize trackability and transmission of "push" force. Different polymers are employed as balloon materials, permitting accurate sizing, conformability to angulated lesions, and dilation of rigid lesions with pressures of greater than 20 atmospheres. There have been substantial concomitant improvements in the quality of radiographic imaging in the cardiac catheterization laboratory. The development of high-resolution fluoroscopy, digital image reconstruction, and on-line computerized quantitative analysis permits clear visualization of small diameter guidewires and catheters within the vasculature, the use of high-definition frozen frames as coronary "road maps," accurate assessment of luminal dimensions before and after

revascularization, and improved detection of vascular wall dissection or thrombus formation.

A stent is a metal prosthetic device that is permanently implanted within a diseased blood vessel to provide a scaffold for disruptions of the vascular wall and prevent elastic recoil and remodeling. Stent designs may be mesh structure, coil, slotted tube, or ring shapes. A substantial body of observational data supports the efficacy of stents as a means of reversing acute mechanical complications of balloon angioplasty and achieving an improved immediate angiographic result. More importantly, randomized clinical trials have shown that these devices reduce the incidence of angiographic restenosis and the need for repeat revascularization procedures compared with balloon angioplasty. Accordingly, stents represent the most important nonpharmacologic advance in the field of interventional cardiology since the introduction of balloon angioplasty and are used in the majority of percutaneous revascularization procedures worldwide.

Currently, more than 50 different types of stents are in clinical use or under investigation. Stents have also been developed for specialized applications, such as the treatment of bifurcations, ostial lesions, or aneurysms or perforations. Most stents are balloon expandable, crimped by the manufacturer in a collapsed form on a deflated angioplasty balloon and deployed at the coronary stenosis by balloon inflation. Self-expanding designs use specialized delivery catheters, with deployment of the stent by withdrawal of a constraining sheath.

Drug-eluting stents are coated with medications that are released into the bloodstream and the surrounding vessel wall. A polymer matrix serves as an interface between the stent and the medication. This method of local drug delivery provides the advantage of minimizing side effects of the pharmacological agent because systemic concentrations remain low. In contrast to catheter-based local delivery strategies, the stent-mediated delivery allows for more continuous release over an extended period of time. Multiple variables affect the process of drug elution: the stent design, the coating matrix, the drug itself, and the vessel wall. Ideally, stents with larger surface areas, smaller gaps between cells, and less postdeployment deformation would enhance the process of drug delivery. The drug-eluting stents in current clinical use are conventional stent models and were not designed for maximizing drug delivery. Ideally, the coating matrix, which modulates the kinetics of drug elution, would be biologically inert and durable. Durability is important because any degradation of the polymer that serves as the coating matrix may cause local inflammation and thereby accelerate the process of in-stent restenosis. The sirolimus- and paclitaxel-eluting stents in current clinical practice employ a synthetic polymer as a coating matrix. The sirolimus-eluting Cypher stent is coated with a mixture of two polymers in a 2:1 ratio, polyethylene-co-vinyl acetate and poly *n*-butyl methacrylate. These polymers are coated onto a stainless steel BX Velocity stent. The polymer in the paclitaxel-eluting Taxus stent is a poly (styrene-b-isobutylene-b-styrene) and is mounted on an Express stainless steel stent. Desirable properties of the medication itself are antiproliferative efficacy and homogeneous diffusion. Drug kinetics may also be affected by the size of the molecule, the hydrophobicity, and the extent of protein binding. In both the Cypher and Taxus stents, most of the drug release into the vessel wall occurs during the first month.

Technique

Patients receive antiplatelet and antithrombin therapy, and arterial access is via percutaneous femoral, brachial, or radial puncture. At some institutions, a pulmonary artery catheter is placed for monitoring of right heart pressures for high-risk patients. The coronary ostium is engaged with a suitable guide catheter, and a steerable coronary guidewire is manipulated under fluoroscopic guidance across the stenosis. A majority of procedures involve stent implantation. In cases of suitable anatomy, direct stenting without predilation may be performed. In these cases, the balloon catheter with the stent preloaded on the outer surface of the balloon is advanced across the guidewire to the lesion and inflated to a pressure at which the stent is fully expanded (typically at 12 to 16 atmospheres). An inadequate result may require balloon postdilation. Many lesions require balloon dilation before a stent placement is possible (predilation). The predilation ensures that a stent can be passed through the stenosis and that it can be completely expanded. Following attempted predilation, inadequate improvement in the degree of stenosis may be treated by repeat balloon inflations, exchange for a balloon catheter of larger inflated diameter, or debulking by an atherectomy device. A minority of stenoses are not suitable for stenting after balloon angioplasty. These lesions are typically in small or tortuous vessels, or in side branches where an ostial stent could compromise the main vessel. In-stent restenosis lesions are best treated by placement of a drug-eluting stent within the prior stent. In most laboratories, intravascular ultrasound imaging is not routinely used after stent placement but may be used in select cases to detect lesion characteristics, such as calcification or dissection, or to confirm the adequacy of stent expansion.

After the angioplasty procedure, patients are generally observed overnight in an inpatient cardiology unit for the infrequent development of recurrent myocardial ischemia or hemorrhagic complications. Postprocedural ischemia, particularly if prolonged and associated with electrocardiographic changes, usually necessitates urgent repeat angiography and revascularization. Routine long-term follow-up is not uniform but should include risk factor modification and surveillance for recurrent ischemia. Functional testing after routine percutaneous coronary intervention (PCI) was not associated with clinical benefit in the Routine versus Selective Exercise Treadmill Testing after Angioplasty (ROSETTA) registry.[4]

Pharmacotherapy

The two major targets of adjunctive pharmacotherapy before, during, and after PCI are the platelet and the coagulation cascade. The benefits of the antiplatelet and antithrombin medications need to be weighed against their increased bleeding risks. All patients receive aspirin before PCI and then indefinitely after the procedure. For long-term therapy, the daily dose of 81 mg appears to provide the optimal balance between efficacy and safety. Patients with documented aspirin allergy receive clopidogrel instead. Because a majority of angioplasty procedures now include stenting, patients receive a loading dose of clopidogrel followed by at least 4 weeks of therapy (at a daily dose of 75 mg). In cases of balloon angioplasty without stenting, it is unclear if a thienopyridine adds benefit beyond that of aspirin alone. Patients with clopidogrel

allergy receive ticlopidine instead. Ideally, the loading dose should be administered at least 2 hours before the PCI,[5] but this is not always feasible. The optimal loading dose is not known. Some reports and one small randomized trial suggest that a 600 mg loading dose may be superior to 300 mg for suppression of ischemic events without an increased risk of bleeding.[6] The goal of the loading dose is to rapidly achieve therapeutic levels of inhibition of platelet aggregation (IPA). More investigation is required to define the optimal (from both efficacy and safety perspectives) level of IPA to support PCI.

The optimal duration of dual antiplatelet therapy (aspirin + clopidogrel) after PCI is unknown. The Clopidogrel for the Reduction of Events During Observation (CREDO) trial demonstrated in patients undergoing PCI (with bare metal stenting) that clopidogrel use beyond the traditional 1 month and through 1 year was associated with further clinical benefit.[7] These findings were consistent with the clinical benefit of long-term clopidogrel therapy observed in the PCI-Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study, which also predated the era of drug-eluting stenting.[8] Based on these findings, many operators continue dual antiplatelet therapy for 1 year in patients who have undergone PCI with a bare metal stent and who are not at an increased bleeding risk. Multiple case reports have described the occurrence of a stent thrombosis years after drug-eluting stent (DES) placement and shortly after the discontinuation of clopidogrel.[9] These reports raise the possibility that it may be beneficial to continue clopidogrel therapy for patients with a DES even years after its placement. More information is required, however, before any recommendations can be made about this issue.

The platelet glycoprotein (GP) IIb/IIIa receptor antagonists provide platelet inhibition beyond that achieved with aspirin and clopidogrel. A sizable body of evidence demonstrates that abciximab, the first of these compounds, reduces periprocedural ischemic events and likely reduces long-term mortality following PCI.[9] Treatment with eptifibatide has also been associated with reduced periprocedural ischemic events.[10] The combination of GP IIb/IIIa blockade with low-dose weight-adjusted heparin thus became the standard therapy for suppression of ischemic complications after PCI, albeit at a somewhat increased risk for bleeding complications. However, a randomized trial failed to demonstrate incremental benefit of abciximab among patients undergoing stenting with a regimen of high-dose heparin and pretreatment (of at least 2 hours) with 600 mg of clopidogrel, although high-risk patients were excluded from this study.[11,12] More importantly, a large-scale study using the direct thrombin inhibitor bivalirudin (see later) instead of heparin demonstrated that similar ischemic outcomes with less bleeding could be achieved using GP IIb/IIIa blockade only in a provisional, rather than planned, fashion[13] in elective or urgent PCI. Administration of abciximab during PCI for acute coronary syndromes (or perhaps for an angiographically visible thrombus) remains the standard of care.

During coronary angioplasty, the advancement of guidewires, balloon catheters, and other devices into the coronary arteries requires anticoagulation to prevent iatrogenic thrombosis. This has traditionally been achieved with intravenous unfractionated heparin with the target activated clotting time of >250 to 300 seconds. However, some operators use the low-molecular-weight heparin enoxaparin as adjunctive anticoagulation in PCI. Bivalirudin, a direct thrombin inhibitor, has been introduced into contemporary interventional practice by the findings of the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial of 6010 patients undergoing elective or urgent PCI.[13] This study established that a strategy of bivalirudin with provisional GP IIb/IIIa (that is, used in the event of a procedural complication) was not inferior to unfractionated heparin plus planned GP IIb/IIIa inhibitor use with respect to ischemic outcomes, and superior in terms of bleeding complications.

Pathophysiology

The mechanisms by which coronary angioplasty may improve vessel luminal dimensions have been characterized by studies in animal models and human cadaveric specimens and by intravascular ultrasound imaging. The radial force exerted by balloon dilation within a coronary artery universally produces endothelial denudation with variable degrees of fracture and separation of plaque from the underlying media, stretching of the medial and adventitial layers, and fracture or dissection of the media. On the basis of these findings, Waller[14] has postulated five different mechanisms for the hemodynamic benefit derived from balloon angioplasty; for any particular lesion one or more of these mechanisms may be operative. *Plaque compression* appears to play only a minor role in the improvement of the dense fibrocalcific stenoses typically present in advanced coronary artery disease. A major mechanism of balloon angioplasty appears to be *plaque fracture*, with immediate formation of fissures within the atherosclerotic lesion that provide channels for blood flow; the ultimate luminal geometry and extent of enlargement are influenced by subsequent plaque healing and remodeling. Additional expansion in the cross-sectional area is obtained when more extensive arterial injury results in localized *medial dissection*. *Stretching* may also occur, providing an immediate improvement of luminal diameter, which may be partially or completely attenuated, however, by elastic recoil. Similarly, vessels in which an eccentric plaque is dilated may be enlarged simply as a result of *stretching of plaque-free arterial segments* with little or no fracture or compression of plaque; early loss of luminal dimensions is due to gradual relaxation of the overstretched segment.

With the deployment of stents, additional pathophysiological considerations arise. In animal models, three somewhat distinct phases in the vascular response to stent implantation may be appreciated by serial observations.[15,16] The thrombotic phase, occurring within the first hours to days, is characterized by formation of extensive platelet- and fibrin-rich thrombus over and surrounding the stent struts. This is followed by a cellular recruitment phase, occurring 3 to 9 days after injury, marked by re-endothelialization and infiltration of the thrombus by monocytes and lymphocytes from the luminal surface outward. These cells secrete growth factors that stimulate smooth muscle cell migration and proliferation. In the final proliferative phase, colonization of the thrombus and resorption of fibrin by smooth muscle cells occur, eventually replacing the thrombus with a neointimal mass. A limited number of stents subsequently retrieved from patients undergoing coronary artery bypass surgery showed deposition of platelets, fibrin, and leukocytes during the first

3 to 7 days following implantation, with subsequent ingrowth of varying degrees of neointima by 3 to 10 months.[17,18] Another important consideration with stenting is possible axial displacement of plaque at the proximal and distal edges. This may occur either immediately or manifest later as restenosis.

Outcome

By the end of the 1980s, the procedural success rate with balloon angioplasty had reached more than 90% in highly selected patients.[19,20] The majority of patients treated with coronary angioplasty experience substantial immediate relief of symptoms of myocardial ischemia. The procedure has been estimated to be effective in decreasing or eliminating angina in 88% and 76%, respectively, of patients,[21] with improvement or resolution of ischemic signs on exercise stress testing.[22] The extent of improvement in symptom status is better among patients with single-vessel coronary artery disease than among those with multivessel involvement.[23,24] Major ischemic complications occur infrequently during coronary angioplasty. With the greater use of stents in the 1990s, the incidence of emergency bypass surgery fell to 0.3%.

Among patients who have undergone initially successful percutaneous revascularization, outcome over the first 6 to 12 months is influenced primarily by the development of recurrent stenoses at treated sites (*restenosis*), whereas events over the longer term appear dependent on progression of atherosclerotic disease. Recurrence of ischemic signs or symptoms among patients treated with coronary angioplasty appears to occur primarily over the first year after the procedure.

Abrupt Vessel Closure

An important determinant of ischemic complications associated with coronary angioplasty is the occurrence of *abrupt vessel closure*, the sudden occlusion of the target or adjacent segment of a coronary vessel during or after percutaneous revascularization. The reported incidence of abrupt closure with balloon angioplasty has ranged from 4.2% to 8.3%.[25-28] Although relatively infrequent, abrupt vessel closure has important clinical sequelae: rates of death, myocardial infarction, and emergency bypass surgery have been reported to range as high as 8%, 54%, and 72%, respectively.[29] Long-term ischemic event rates have also been shown to be elevated among patients who have suffered even transient abrupt closure.[30]

The pathophysiological mechanisms of abrupt coronary occlusion are similar to those that produce the therapeutic benefit derived from balloon dilation. Although plaque and medial fissuring induced by balloon angioplasty usually remain localized, extensive disruption of the medial layer can occur, leading to obstructive dissection flaps or intramural hematoma. Exposure of subendothelial vascular wall components results in platelet deposition and activation with formation of thrombin; occlusive thrombosis may occur, often in association with blood stasis produced by medial dissection flaps. In some patients, particularly those with unstable ischemic syndromes, propagation of preexistent mural thrombus at the treatment site may be the predominant mechanism of coronary obstruction.

A number of preventive measures may limit the occurrence of abrupt vessel closure during PCI. Pharmacological approaches focus on suppression of platelet aggregation and thrombus formation at the site of balloon dilation or on pre-procedural resolution of pre-existent mural thrombus. Procedural mechanical factors that may reduce the risk of abrupt closure include selection of appropriately sized balloons to avoid excessive overdilation relative to the normal coronary diameter,[31,32] the use of long (30 to 40 mm) balloons for angulated or diffuse lesions, or prolonged inflations,[33,34] and stent placement.

If abrupt closure occurs, stent implantation is usually successful in this setting, by virtue of its "scaffolding" effect at the disrupted angioplasty site; other ablative devices have also been occasionally employed. Administration of platelet GP IIb/IIIa antagonists may be particularly effective in patients with thrombotic coronary occlusion.[35] The preponderance of published data, however, suggests that fibrinolytic agents such as urokinase are of limited or no usefulness.[27,28,36] When emergency surgical revascularization is required, perioperative death and myocardial infarction occur more frequently than would be expected for comparable patients managed by primary elective surgery, with published mortality rates ranging from 1.4% to 19% and perioperative Q-wave infarction rates from 20% to 57%.[37]

The most effective means to prevent acute vessel closure is to use a stent in a planned fashion. However, when PTCA is performed *without planned* stent placement, bailout or unplanned stent placement for abrupt or threatened coronary closure is a highly effective means of improving procedural outcome and reducing the risk of ischemic complications. By virtue of their ability to "tack down" obstructive dissection flaps, minimize contact between blood and thrombogenic subintimal arterial wall components, limit elastic recoil or spasm, and optimize blood flow dynamics, stents produce excellent angiographic resolution of acute coronary occlusion or major dissection. Despite some early concerns, with contemporary techniques of deployment and antithrombotic therapy, stenting can be expected to reverse abrupt vessel closure in a large proportion of cases with low rates of ischemic complications.

Restenosis

The principal factor limiting the long-term benefit of PCI (with or without stenting) is restenosis, the angiographic renarrowing of the vessel lumen following successful balloon dilation of a vascular lesion. The reported incidence of restenosis (before the era of drug-eluting stents) ranged from 30% to 50%, depending on the method of follow-up and the criteria used to define restenosis. The most common clinical manifestation of restenosis is recurrence of anginal chest pain.[31,38] Myocardial infarction as the first indication of restenosis is rare, and it has been speculated that the fibroproliferative restenotic lesion is less likely than the lipid-laden native atherosclerotic plaque to undergo plaque rupture.[39] The presence of angiographic restenosis has only limited predictive value for the occurrence of clinical events—with up to 30% of patients with restenosis found to be asymptomatic.[38,40,41] The apparent discordance between clinical outcome and angiographic restenosis is probably related to the influence of collateral vessels,[40] incomplete revascularization, or progression of atherosclerotic disease in other arteries, as well as to the limitations of a dichotomous definition of

restenosis. Moreover, estimation of the true *functional* severity of stenoses by angiography may be problematic, as has been suggested by intravascular ultrasound and Doppler flow studies. Repeat revascularization of patients with angiographic restenosis is generally reserved for those with clinical symptoms or demonstrable ischemia because the prognosis in asymptomatic patients is quite favorable.[40,42]

The pathogenesis of restenosis is complex and multifactorial. Restenosis within lesions that do not show evidence of intimal hyperplasia may result, in part, from stretching of atherosclerotic plaque or of disease-free arterial wall (in eccentric lesions) during balloon dilation, followed by elastic recoil.[43] More importantly, however, chronic shrinkage or "remodeling" of the arterial cross-sectional area has been shown to occur after balloon dilation, with pathological findings in animal models demonstrating structural changes extending throughout the arterial wall.[44,45] Serial intravascular ultrasound studies in humans also support the concept that remodeling is an important mechanism of restenosis after balloon angioplasty.[46]

Another major mechanism of restenosis is intimal fibrous hyperplasia. The magnitude of this response, and hence the amount of proliferative tissue, appear to be proportional to the degree of arterial injury during percutaneous revascularization.[47,48] The cascade of events leading to the formation of the neointimal proliferative lesion seems to be initiated by endothelial denudation, plaque disruption, and exposure of subendothelial components, leading to platelet deposition and thrombus formation. Growth and chemotactic factors released from platelets, inflammatory cells, endothelium, and smooth muscle cells induce proliferation and migration of vascular smooth muscle cells from the arterial media to intima, synthesis of extracellular collagen and proteoglycan matrix, and excessive fibrocellular accumulation.[47,49-52] The mechanisms by which stents reduce the incidence of restenosis appear to be by improvement in the immediate angiographic result (better acute gain in luminal diameter), as well as by prevention of early elastic recoil and chronic negative remodeling. Restenosis within a stent occurs exclusively by neointimal hyperplasia and ingrowth between stent struts,[53,54] a process that is not diminished, and is, in fact, increased by stenting relative to balloon angioplasty.[55] Luminal diameter within a stent typically decreases over 6 months after implantation due to neointimal hyperplasia, with evidence of modest regression of stenosis thereafter over 3 years of follow-up.[56]

Sirolimus and paclitaxel are the bioactive compounds of the two drug-eluting stents in current clinical use (Fig. 6–1). Sirolimus is a macrolide antibiotic with both immunosuppressive and antimitotic activities. It binds FK binding protein in the vessel wall smooth muscle cell cytosol, and that complex then binds the mammalian target of rapamycin (mTOR)—inhibiting its activation and ultimately leading to arrest of cell cycle in the G_1 phase. This process corresponds to inhibition of smooth muscle cell growth, retarding the process of neointimal proliferation and in-stent restenosis. Paclitaxel, a lipophilic molecule derived from the Pacific yew tree *Taxus brevifolia,* acts via stabilizing microtubules and has known anti-tumor action (it is the active ingredient in the widely used chemotherapy drug Taxol). It shifts the cytoskeletal equilibrium toward decreased cell proliferation. Retrospective studies have identified several clinical, lesion morphological, and procedural factors that may influence the risk of restenosis following PCI, although the associations among many of these features and restenosis have been variable. Among the clinical factors, only the presence of unstable angina,[57-60] variant angina,[61] and diabetes mellitus[38,58,59] have consistently predicted an elevated incidence of restenosis. Factors associated with an increased risk of in-stent restenosis include stenting of restenotic or saphenous vein graft lesions or total occlusions, lesion length, multiple stents, greater residual stenosis, diabetes mellitus, and smaller reference vessel diameter.[62] Rates of restenosis and target vessel revascularization after stenting of these higher risk lesions have been shown to be 2 to 4 times greater than with stenoses that meet the restricted criteria of the original Benestent and STRESS trials.[63] To date, the factors that have been associated with in-stent restenosis in the drug-eluting stent era are diabetes mellitus, small vessel size, and lesion length.[64]

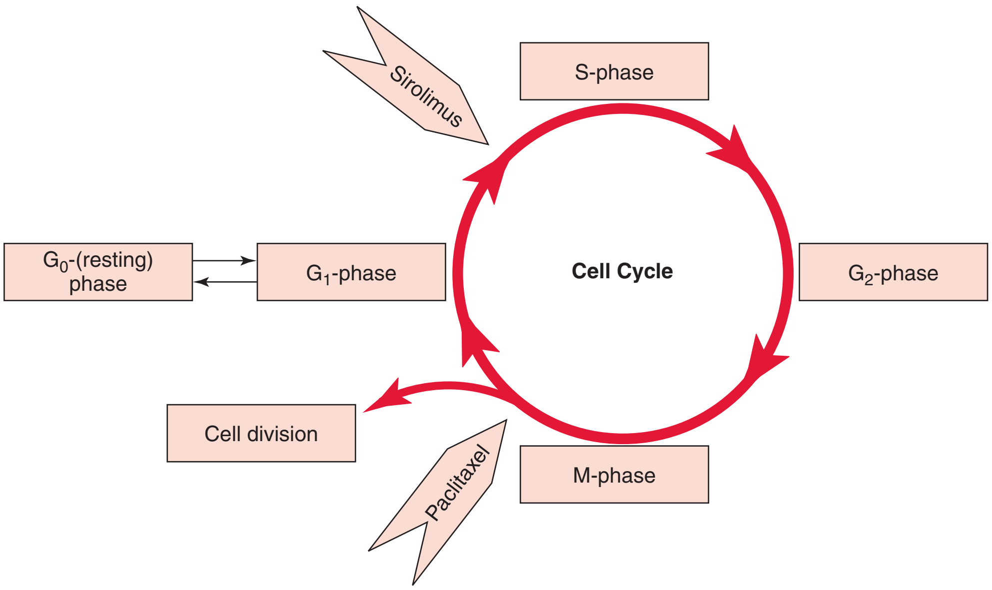

Figure 6–1 Sirolimus and paclitaxel inhibit the cell cycle during the G_1- and M-phases, respectively.

Notwithstanding the efficacy of stenting to prevent or treat abrupt closure, the widespread clinical application of this technology has been motivated primarily by the impact of stents on the incidence of restenosis. Two seminal randomized trials compared placement of the Palmaz-Schatz stent with conventional balloon angioplasty in a highly select group of patients with de novo native coronary stenoses, providing the first compelling evidence that these devices can reduce the frequency of repeat revascularization procedures and angiographic restenosis.[65,66] Subsequent studies confirmed these findings among patients with a broader spectrum of clinical syndromes and coronary lesion morphologies, including those with chronic total occlusions, restenotic lesions, and saphenous vein graft stenoses.[67-73] Over long-term follow-up (6 to 12 months) in these trials, rates of ischemic events were reduced by 34% to 76% by stenting compared with balloon angioplasty, coupled with 20% to 57% reductions in angiographic indices of restenosis. Importantly, long-term clinical benefit observed in these studies was confined to reductions in the need for repeat target vessel revascularization procedures or recurrent ischemia, and no trial has shown a convincing suppression by stents of the long-term risk of death or myocardial infarction. These findings of randomized stent trials have been confirmed by observational reports of clinical practice. A database analysis of 9594 percutaneous interventional procedures performed in British Columbia, Canada, between 1994 and 1997 showed a significant decrease in the rate of adverse cardiac events by 1 year, due exclusively to a reduction in the incidence of repeat target vessel revascularization (24.4% to 17.0%, $P < 0.001$), concordant with a rise in the rate of stent use from 14% to 59% over the same time period.[74]

Although the ingrowth of neointima is usually responsive to repeat balloon dilation within the stent, rates of recurrence are high. In the U.S. Palmaz-Schatz registry, recurrence of stenosis was observed in 54% of patients treated for in-stent restenosis.[75] The risk of recurrent restenosis appears to be related to the pattern of in-stent luminal narrowing, ranging from 10% to 31% with focal narrowings to as high as 63% to 88% with diffuse in-stent restenosis.[76,77] A large number of pharmacological agents have been tested that might be expected to influence favorably different components of the arterial response to injury,[78] but clinical trials have almost uniformly failed to demonstrate an unequivocal reduction in the incidence of restenosis with systemic pharmacological therapies. The treatment of choice for in-stent restenosis is repeat PCI with placement of one or more drug-eluting stents within the stenosed stent. Kastrati and colleagues demonstrated in the 300-patient Intracoronary Stenting and Angiographic Results—Drug-Eluting Stents for In-stent Restenosis (ISAR-DESIRE) randomized trial that patients whose in-stent restenosis was treated with a drug-eluting stent had a lower rate of angiographic restenosis and a lower need for subsequent target vessel revascularization compared with patients treated with a bare metal stent.[79] The rate of angiographic restenosis of ≥50% 6 months after the PCI was 14.3% and 21.7% among patients treated with sirolimus- and paclitaxel-eluting stents, respectively, and 44.6% among patients in the bare metal stent group ($P \leq 0.001$ for both comparisons of drug-eluting stent with bare metal stent).

Drug-Eluting Stents and Restenosis

The emergence of drug-eluting stents (DES) has been a major advance in the struggle against in-stent restenosis. Both sirolimus- and paclitaxel-eluting stents have been shown to reduce the incidence of angiographic and clinical measures of restenosis. The first-in-man study of the sirolimus-eluting stent (SES) demonstrated that, in 45 patients with angina pectoris and native coronary artery lesions, angioplasty with SES was safe with no cases of in-stent restenosis at 24 months.[80] These encouraging findings set the stage for the first randomized trial comparing SES with the identical BX Velocity stent without the coating (thus referred to as *bare*) among 238 patients with simple angiographic stenoses (Table 6–1). The RAndomized study with the sirolimus-eluting BX VELocity balloon-expandable stent (RAVEL) demonstrated a remarkable zero percent incidence of binary restenosis (defined as 50% stenosis) and no loss of luminal area at 6 months after stenting among a very low-risk group of patients treated with the SES, compared with a 26.6% restenosis rate and a mean 0.80 mm late loss of luminal dimension in the control group.

In concert with the angiographic findings, the sirolimus stent group also had a lower rate of target vessel revascularization (TVR) at up to 12 months of follow-up compared

Table 6–1 Clinical and Angiographic Outcomes in Bare Metal Stent versus Drug-Eluting Stent Randomized Trials

Trial	F/U	Number	TLR BMS (%)	TLR DES (%)	*P*-Value	Late Loss BMS (mm)	Late Loss DES (mm)	*P*-Value
RAVEL	6 mo	238	23.7*	0*	<0.001	0.80	–0.01	<0.001
SIRIUS	9 mo	1058	16.6*	4.1*	<0.001	0.81	0.24	<0.001
E-SIRIUS	6 mo	352	20.9	4.0	<0.0001	0.80	0.19	<0.0001
C-SIRIUS	8 mo	100	18.0	4.0	0.05	0.79	0.12	<0.001
TAXUS I	12 mo	61	10.0	0	0.24	0.71	0.36	<0.01
TAXUS II	12 mo	536	12.9†	4.7†	0.03	0.79†	0.31†	<0.0001
TAXUS IV	9 mo	1314	12.0*	4.7*	<0.001	0.61	0.23	<0.001
TAXUS V	9 mo	1172	15.7	8.6	<0.001	0.60	0.33	<0.0001
TAXUS VI	9 mo	448	18.9	6.8	0.0001	0.66	0.24	<0.0001

*Refers to target vessel revascularization.
†Refers to slow-release kinetic stents.
BMS, bare metal stent; DES, drug-eluting stent; F/U, follow-up; TLR, target lesion revascularization.

with the bare metal stent (BMS) group (0% versus 23.7%, $P < 0.001$).[81] The SIRolImUS-coated BX Velocity stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) trial confirmed the results of the RAVEL trial in a larger study with broader inclusion criteria.[82] The patients ($n = 1058$) were randomized to receive a sirolimus-eluting stent versus a bare metal stent, with the primary endpoint a combination of death, myocardial infarction, or TVR within 9 months. The sirolimus group had a lower incidence of primary endpoint, driven by the reduced need for TVR (4.1% versus 16.6%, $P < 0.001$). The E-SIRIUS trial ($n = 352$) extended these findings to patients with longer lesions in smaller vessels.[83] Treatment with sirolimus-eluting stent was associated with less binary in-stent restenosis (5.9% versus 42.3%, $P = 0.0001$) and less target lesion revascularization (4.0% versus 20.9%, $P < 0.0001$) at 8 months compared with bare metal stenting. Similar results were noted in the C-SIRIUS trial.[84] The benefit of the sirolimus-eluting stent use has also been demonstrated in a real-world registry. The Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry compared consecutive patients ($n = 508$) who received sirolimus-eluting stents with those who had been treated with bare metal stents ($n = 450$) prior to the availability of SES.[85] Although the SES group was at higher risk for ischemic outcomes than the BMS group, based on clinical and angiographic characteristics, the rate of clinically driven target vessel revascularization at one year was much lower in the SES group (3.7% versus 10.9%, $P<0.001$).

Paclitaxel-eluting stents (PES) have also demonstrated clinical benefit in randomized trials. The TAXUS I trial evaluated slow-release TAXUS NIRx stent versus bare NIR stent in 61 patients with simple coronary lesions.[86] The angiographic measures of restenosis were reduced in the TAXUS stent group. In the TAXUS II trial, 536 patients were randomized to TAXUS stent versus an identical bare metal stent that served as the control.[87] Angiographic and intravascular ultrasound indices of restenosis, as well as the rate of target lesion revascularization, were reduced in the TAXUS stent groups compared with the control groups. The largest PES trial to date, the TAXUS IV trial, randomized 1314 patients undergoing PCI with stenting of a single, previously untreated native coronary artery lesion to slow-release TAXUS EXPRESS stent versus bare EXPRESS stent.[88] The rate of ischemia-driven TVR at 9 months was lower in the PES group compared with the BMS group (4.7% versus 12.0%, $P < 0.001$) and the angiographic endpoints characterizing in-stent restenosis were similarly reduced in the PES group.

The TAXUS V trial included patients with long coronary lesions (up to 46 mm) and lesions in small vessels (down to a diameter of 2.25 mm).[89] This 1172-patient trial reported a lower rate of major adverse cardiac events (death, myocardial infarction, or target vessel revascularization) at 9 months in the TAXUS group compared with the bare metal stent group: 15.0% versus 21.2%, $P = 0.008$). This was driven by a lower rate of target *lesion* revascularization in the TAXUS group (8.6% versus 15.7%, $P < 0.001$).

The TAXUS VI trial used the moderate-release formulation paclitaxel-eluting stent and studied 448 patients with long lesions (up to 40 mm). The primary endpoint of the study, the rate of target vessel revascularization at 9 months, was lower in the TAXUS stent group compared with the BMS group: 9.1% versus 19.4%, respectively, $P = 0.003$. Of note, this rate in the overlapping stent subgroup was reduced from 24.6% in the control group to 1.6% in the TAXUS stent group ($P < 0.0001$). In summary, the TAXUS V and VI trials have extended the benefits of the paclitaxel-eluting stent to a group of patients with more complex coronary lesions.

The sirolimus- and paclitaxel-eluting stents have been compared in several clinical trials (Table 6–2). In the REALITY trial, the angiographic endpoint of late loss favored SES compared with PES.[90] The SIRTAX trial demonstrated lower rates of late loss, restenosis, and TLR with SES.[91] Similarly, the ISAR-Diabetes trial revealed a lower rate of late loss and restenosis among diabetics treated with SES.[92] The ISAR-DESIRE trial evaluated patients with in-stent restenosis (with prior bare metal stent).[79] The rate of target vessel revascularization at 6 months after PCI was lower in the SES group compared with the PES group, but there was no statistically significant difference in the rate of restenosis. Kastrati and colleagues recently published a meta-analysis of six randomized trials[79,90-94] comparing the sirolimus-eluting stent with the paclitaxel-eluting stent.[95] The incidence of target lesion revascularization was less frequent among patients randomized to SES compared with PES (5.1% versus 7.8%, odds ratio 0.64, $P = 0.001$). Likewise, angiographic restenosis was less frequent with SES versus PES (9.3% versus 13.1%, odds ratio 0.68, $P = 0.001$). These early comparative studies between SES and PES show that there is less late loss with SES, although the impact on clinical revascularization rates varies. The emerging consensus is that, in cases of high-risk lesions, late loss is a significant issue and SES implantation is recommended (Fig. 6–2).

OTHER DEVICES

Devices that remove atheromatous material are used as adjuncts in coronary angioplasty. The directional atherectomy

Table 6–2 Clinical and Angiographic Outcomes in Sirolimus- versus Paclitaxel-Eluting Stent Randomized Trials

Trial	F/U	Number	TLR SES (%)	TLR PES (%)	*P*-Value	Late Loss SES (mm)	Late Loss PES (mm)	*P*-Value
REALITY	8 mo	1353	5.0	5.4	0.81	0.09	0.31	<0.001
SIRTAX	9 mo	1005	4.8	8.3	0.25	0.13	0.25	0.013
ISAR-Diabetes	6 mo	250	6.4	12.0	0.13	0.43	0.67	0.002
ISAR-DESIRE	6 mo	300	8.0*	19.0*	0.02	0.10	0.26	0.004

*Refers to target *vessel* revascularization.
F/U, follow-up; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; TLR, target lesion revascularization.

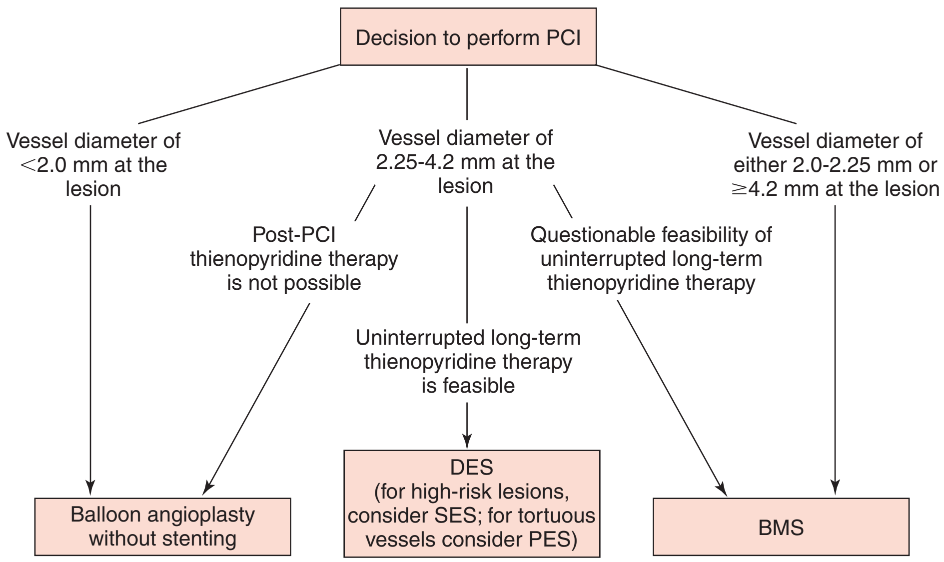

Figure 6–2 The decision to implant a bare metal stent (BMS), a drug-eluting stent (DES), or no stent at all depends on vessel size and the prospects of thienopyridine therapy. PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.

catheter cuts the stenosis using a spinning blade, while rotational atherectomy abrades and pulverizes the plaque. Distal embolic protection devices are positioned downstream of the site of angioplasty and collect embolizing plaque material before it reaches the myocardial microvasculature. Transluminal extraction atherectomy, cutting balloon, rheolytic thrombectomy, and excimer laser are used less commonly in the current practice. Intracoronary irradiation (brachytherapy), a common treatment for in-stent restenosis in the past, is now infrequently used with the emergence of drug-eluting stents (Fig. 6–3).

Atherectomy

The directional coronary atherectomy catheter consists of a metal cylinder at its distal end which houses a coaxial rotating cup-shaped blade. After multiple atherectomy cuts, most patients require adjunctive balloon angioplasty and stenting to achieve an optimal angiographic result. Plaque removal by directional atherectomy may produce an angiographic result that is superior to that obtainable by PTCA, particularly for lesions that are eccentric, ostial, restenotic, or associated with intraluminal thrombus.[96,97] Failures of atherectomy are most frequently due to inability to pass the bulky catheter to or across the coronary stenosis, although other complications include coronary occlusion, embolization, or perforation. Directional atherectomy is time-consuming and technically demanding, and a substantial operator learning curve exists. In contrast, stenting does not require large vascular access sheaths, and it can be conducted quickly and relatively easily. Directional atherectomy may be best suited for certain lesion subsets less amenable to stenting, such as bifurcation lesions, ostial stenoses, or in-stent restenosis.

The rotational atherectomy catheter uses a rapidly spinning abrasive tip welded to the end of a flexible metal drive shaft to grind the internal lumen of an atherosclerotic plaque. The distal end of the catheter consists of an elliptical metal burr coated with diamond chips that rotates while it is slowly advanced across the atherosclerotic plaque. Rotational atherectomy theoretically operates on the principle of differential cutting, whereby rigid material such as calcium or fibrotic plaque is preferentially pulverized rather than the elastic components of the arterial wall.[98] As such, this technique has been particularly advocated for heavily calcified, inelastic or "nondilatable," eccentric, and diffuse coronary lesions. Complications of rotational atherectomy include "slow flow" reflecting distal embolization as well as coronary dissection and perforation. The clinical indication for rotational atherectomy is, therefore, to improve acute procedural success rates in certain coronary lesion subsets that are poorly suited for balloon angioplasty, including heavily calcified vessels, rigid nondilatable stenoses, aortic or branch ostial lesions, and bifurcation stenoses.

Embolic Protection Devices

Downstream embolization of atherosclerotic debris is inevitable to some extent during angioplasty. Such embolization results in increased no-reflow phenomenon, post-procedural myonecrosis, and microvascular dysfunction, all of which are associated with poorer long-term outcome. Much interest has recently focused on mechanical solutions for this challenging problem. The various embolic protection devices (EPD) are positioned distally to the site of angioplasty with the goal of collecting the debris before it reaches the microvasculature. After the procedure, the EPD is removed along with the material that has been intercepted. The two main design types of the various EPDs, either in commercial use or in development, are filters and occlusion balloons. The filter-based systems are nonocclusive and preserve blood flow through small pores (~100 μm). The balloon-occlusion based systems temporarily occlude the distal vessel followed by aspiration of liberated atheromatous and thrombotic material. The challenges with the use of EPD include deliverability of the device in cases of severe stenosis or tortuosity, absence of a suitable distal deployment or "landing" zone, the presence of any side branches between the lesion and the device (that might receive the debris before it reaches the EPD), initial embolization with the manipulation of the wire before the placement of the EPD, and imperfect collection

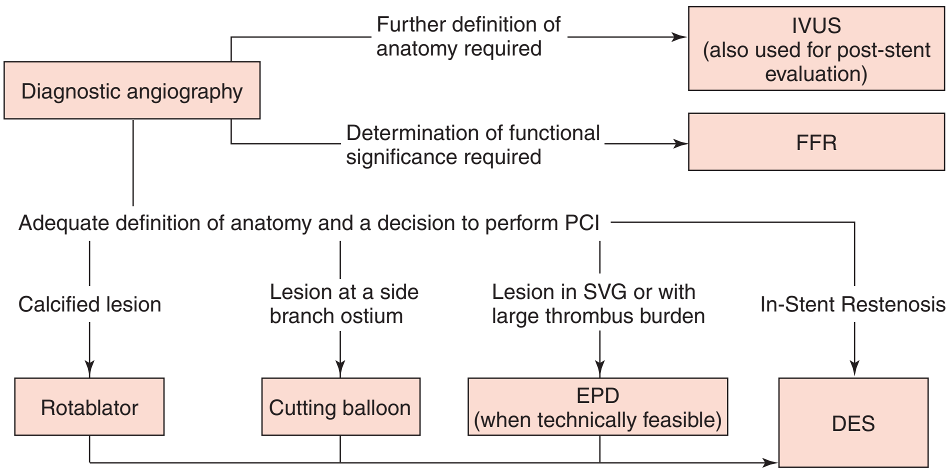

Figure 6–3 Following diagnostic angiography, intravascular ultrasound (IVUS) and pressure wire may be used to obtain further information. Specific lesion characteristics call for the use of rotational atherectomy (abbreviated as "rotablator"), cutting balloon, and distal embolic protection devices (EPD). DES, drug-eluting stent; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; SVG, saphenous vein graft.

with some debris escaping past the EPD and into the microvasculature.

Angioplasty on degenerated saphenous vein grafts (SVGs) is associated with significant embolization burden and thus served as a good clinical test setting for the hypothesis that distal embolic protection would improve clinical outcomes. The Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial randomized 801 patients undergoing PCI on a SVG to the use of PercuSurge GuardWire balloon occlusion device versus standard guidewire.[99] The patients in the EPD group had a lower incidence of post-PCI myocardial infarction (8.6% versus 14.7%, $P = 0.008$) and no-reflow phenomenon (3% versus 9%, $P = 0.02$) compared with the control patients. The FilterWire EX Randomized Evaluation (FIRE) trial compared the FilterWire with the GuardWire in 651 patients undergoing SVG PCI and demonstrated a similar incidence of adverse cardiac events at 30 days.[100] These findings established the utility of distal embolic protection in vein graft angioplasty. Encouraged by the SAFER trial results, the use of EPD in angioplasty for acute myocardial infarction was evaluated in the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial ($n = 501$).[101] Patients were randomized to GuardWire Plus balloon occlusion and aspiration system versus standard therapy, and visible debris was recovered in 73% of the interventions in the distal protection group. There were no differences, however, in microvascular function (as detected by ST-segment resolution), infarct size, or major adverse cardiac events between the two treatment groups. Given that primary PCI appears to carry a high risk of distal embolization, the EMERALD trial results suggest that embolic protection does not have the same benefits in native coronary artery PCI as those observed in vein graft angioplasty. It is possible, however, that improvements in device design might make EPD a beneficial therapy in native coronary artery angioplasty.

An alternate strategy for embolic protection is illustrated by the Proxis embolic protection system. It is the first *proximal* embolic protection system with an occlusive balloon-aspiration system placed upstream to the lesion. On balloon inflation, blood flow in the coronary artery is stopped temporarily, followed by aspiration of material that might otherwise embolize with the upcoming angioplasty.

Endovascular Radiation

Adjunctive intracoronary brachytherapy involves the placement of beta- or gamma-emitting wire ribbons next to the lesion after conventional percutaneous treatment. Following redilation of the in-stent restenosis (ISR), brachytherapy significantly reduces the risk of subsequent recurrence. In the first randomized trial of 54 patients, brachytherapy with a gamma emitter reduced the binary restenosis rate at 6 months (17% versus 54%, $P = 0.01$),[102] with the benefit sustained through 3 years[103] and 5 years, respectively.[104] Coronary brachytherapy using gamma emitter is technically demanding—requiring long dwell times—and is, therefore, rarely used. The STents And Radiation Therapy (START) trial randomized 476 patients with ISR to beta-radiation (Beta-Cath system) versus placebo and documented a reduced rate of angiographic restenosis in the irradiated segments in the treatment arm 8 months after PCI (24% versus 46%, $P < 0.001$).[105] Similar reduction was noted in the rate of target lesion revascularization (8% versus 22%, $P = 0.008$). The Intimal Hyperplasia Inhibition with Beta In-stent Trial (INHIBIT) evaluated the efficacy of the beta-emitting GALILEO system.[106] The primary endpoint of binary angiographic restenosis in the stented segment at 9 months after PCI was reduced by 67% in the treatment arm ($P = 0.0001$), and corresponding reduction was noted in the need for TLR. The anti-proliferative effect of brachytherapy is largely due to a delay in post-PCI healing. Once this effect has dissipated and healing begins (after 2 to 3 years), the process of neointimal hyperplasia may resume. The emergence of drug-eluting stents has made the use of brachytherapy quite rare. It is important to recognize, however, that vascular brachytherapy was the first effective antiproliferative treatment for in-stent restenosis.

INTRAVASCULAR IMAGING TECHNIQUES

Despite improvements in the resolution of coronary radiographic imaging, there remain inherent limitations to the use of angiography as a means of assessing coronary lesion morphology and the results of percutaneous revascularization. Coronary angiography visualizes only the opacified lumen of

the artery and is thus incapable of evaluating pathological structures within the vascular wall. Substantial atherosclerosis may develop before a reduction in luminal dimensions,[107] a process that cannot be discerned by angiographic assessment. The two-dimensional view provided by the coronary angiogram is often inadequate to appreciate the severity of eccentric or complex lesions and underestimates the degree of stenosis in the presence of diffuse coronary disease extending into adjacent "normal" segments. New modalities have thus been applied in the setting of percutaneous coronary intervention to visualize more precisely the arterial wall and the vascular lumen or to assess the functional significance of a coronary stenosis.

Intracoronary Pressure Measurement

Technical advances have led to the development of coronary guidewires with microminiaturized, solid-state pressure transducers at their tips (Radi, Uppsala, Sweden and Endosonics, Rancho Cordova, CA), allowing measurement of high-fidelity pressure gradients across a coronary lesion with the same platform used for delivery of coronary interventional devices. The pressure wire provides a physiological assessment of the functional significance of a coronary stenosis through derivation of a parameter known as fractional flow reserve (FFR). FFR is the ratio of maximal hyperemic blood flow in a stenotic artery to the maximal flow that would occur in the absence of a stenosis. This index is determined by precise measurements of pressures proximal and distal to the stenotic lesion during maximal hyperemia induced by adenosine infusion. The FFR value in normal vessels is 1.0, decreasing with increasing stenosis severity. A threshold value of 0.75 for FFR has been correlated with exercise-induced myocardial ischemia,[108] an FFR >0.94 has been associated with optimal stent deployment, and a value >0.90 with an optimal result of balloon angioplasty.

Intravascular Ultrasound

There has been rapid evolution of technology for miniaturization of high-frequency transducers to permit ultrasound imaging from within the coronary vasculature. Ultrasound energy emitted from an intraluminal probe penetrates into the vascular wall, with reflections formed at the interfaces between tissue components of different acoustic properties. Intravascular ultrasound (IVUS) thus produces high resolution cross-sectional images that not only delineate absolute luminal dimensions but also the extent and structure of the atherosclerotic plaque and the arterial wall. IVUS images have been shown to correlate well with histological findings.[109,110]

IVUS has been employed clinically to identify angiographically inapparent atherosclerotic plaque, quantify luminal dimensions, and characterize the composition of stenotic lesions (soft plaque, hard plaque, calcification, thrombus). This technique has been particularly useful in assessing the degree of luminal compromise in lesions that appear to be equivocal or indeterminate by angiography.[111,112] IVUS has contributed to our understanding of the mechanisms of balloon angioplasty[113] and new device interventions[114-116] and has been employed clinically to guide and assess the results of these techniques. Identification of certain morphologic features by ultrasound may predict the outcome of percutaneous intervention[117] and aid in the selection of the best device to obtain an optimal angiographic result.[118]

Serial IVUS examinations may also be performed during the revascularization procedure to assess interim results and guide further interventional therapy. Following percutaneous revascularization, IVUS provides a more accurate estimation of luminal dimensions than does angiography[119] and appears to be the most sensitive method for evaluating the completeness of lesion dilation, plaque removal, or stent deployment and for detecting plaque disruption or medial dissection. IVUS guidance during stent implantation is useful in optimizing postprocedural luminal area and may reduce long-term restenosis. In the CRUISE study, the cross-sectional luminal area after stenting was greater among patients whose PCI involved IVUS guidance compared with angiography guidance (mean 7.14 versus 6.25 mm^2), with a significant reduction in the late incidence of target vessel revascularization (8.5% versus 15.2%, $P < 0.05$).[120] Likewise, a meta-analysis of 9 studies and 2972 patients demonstrated that IVUS-guided PCI with stenting was associated with a lower rate of target vessel revascularization at 6 months (odds ratio 0.62, $P < 0.0001$) after the procedure compared with an angiographically guided approach.[121]

IVUS measurement of coronary artery plaque volume has been used to evaluate the efficacy of anti-atherosclerotic therapy. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, greater reduction in LDL-cholesterol with high-dose atorvastatin compared with pravastatin correlated with greater retardation of atherosclerosis progression as measured by IVUS.

SUMMARY

Over the last quarter of a decade, the development of new and enhanced methods of percutaneous coronary revascularization has led to considerable expansion in indications for this technique and improvements in immediate and long-term outcomes. More than 800,000 interventional procedures are performed in the United States each year, exceeding the number of bypass surgery operations. Although risk factors for acute complications and long-term restenosis certainly influence the selection of percutaneous versus surgical revascularization for individual patients, angioplasty and related device technologies can be applied when appropriate to patients in all age groups, with single-vessel or multivessel coronary artery disease, with preserved or impaired ventricular function, and with simple or complex lesion characteristics. In the hands of skilled operators and at experienced institutions, rates of procedural success should exceed 98%, and the acute complications of death, Q-wave myocardial infarction, or emergency bypass surgery should occur in less than 0.5% of patients. The majority of patients treated by percutaneous revascularization will undergo drug-eluting stent implantation, with the expectation of a 5% rate of symptomatic restenosis requiring repeat target vessel revascularization over the ensuing 9 months. Future developments in this field will be directed at more effective management of difficult coronary stenoses, such as total occlusions or degenerated saphenous vein grafts, or at modification of the adverse arterial thrombotic, proliferative, and remodeling responses that lead to long-term restenosis.

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Chapter 7

Treatment with Drug-Eluting Stents

George D. Dangas

CHAPTER CONTENTS

Because symptoms from coronary stenoses are related to plaques in a coronary artery, a locally applied treatment is a reasonable therapeutic approach. Although coronary stent implantation was introduced to prevent recoil and arterial remodeling (shrinkage) after balloon angioplasty, most adjunctive medical therapy approaches remain systemic. The most successful systemic therapies involve anticoagulation and primary/secondary prevention of coronary artery disease, whereas systemic therapies aimed at restenosis have been unsuccessful. The drug-eluting stent systems have successfully realized the possibility of combining mechanical (stent) support and local drug delivery for the treatment of coronary artery disease.

DRUG-ELUTING STENT SYSTEM

The drug-eluting stent (DES) is an integrated mechanical and pharmacologic unit for local treatment of coronary artery disease. The metallic stent provides the scaffold necessary to prevent vessel recoil and unfavorable remodeling,[1] whereas the eluted drug aims to limit the neointimal proliferation, although other mechanisms may coexist (Table 7–1).

Typically, the drug is eluted from a polymer that is wrapped around a metallic surface. Although alternative types of drug-elution can also be achieved, the approved and best-studied DES systems release their bioactive agents from encapsulated, elastomeric, non-erosive, biostable polymers. The polymer limits, in some ways, the flexibility of the stent itself, thereby making delivery of a DES inside a coronary artery more technically demanding than with an identical bare-metal stent. In addition, the polymer may lead to a late local inflammatory process because it is not dissolved right after drug elution.

RESULTS OF MAIN CLINICAL TRIALS OF APPROVED DES

There are currently three DES systems that are widely used after approval for human use. Overall, the results have been remarkably consistent across DES systems and patient populations. Typically, each DES was first submitted to a small clinical trial of near-ideal isolated lesions, followed by clinical studies in patients with lesions of escalating complexity. Ultimately, unselected registry (so called "real-world") data, subset analyses, and comparative studies between DES have complemented the wealth of clinical research knowledge in the area of DES. In brief, more than 10,000 patients have been studied within this medical subject.

Sirolimus-Eluting Stent

The sirolimus-eluting stent (Cypher) was the first to be approved worldwide. The First-In-Man (FIM) investigational experience with this DES was initiated in December 1999 and a 4-year clinical and angiographic follow-up has confirmed the safety, efficacy, and durability of the clinical results (Fig. 7–1).[2] When evaluated in a multicenter setting, this DES achieved a remarkable absolute "zero" for events in the initial trial: 0 mm late loss, 0% restenosis, 0% repeat target vessel revascularization, and 0% stent thrombosis.[3,4] Such observations were quite novel for the specialty of interventional cardiology that had been accustomed for many years to negative results regarding restenosis prevention in humans with multiple agents and devices despite promising animal data and positive pilot clinical results. This inauguration of the DES "revolution" established a high level of interest on subsequent clinical results with this and other DES systems (Table 7–2).[1,5-13]

Technical Lessons from Sirolimus-Eluting Stent Studies

The pivotal multicenter randomized trial confirmed the profound suppression of neointimal proliferation (mean late lumen loss <0.1 mm, restenosis <10%) with the sirolimus DES.[5] Stent thrombosis and late aneurysm development were rare. Results were excellent within the stent area but not so remarkable in the immediate peri-stent area (i.e., when 5 mm proximal and distal to the stent edge were taken into account). The important observation was made that balloon predilation might have caused a degree of injury at arterial areas not ultimately covered with a DES. This type of "geographical miss" might indeed result in injured arterial areas that were thus prone to neointimal proliferation but did not receive

Table 7–1 Substances Tried as Anti-restenosis Agents on Drug-Eluting Stent Systems

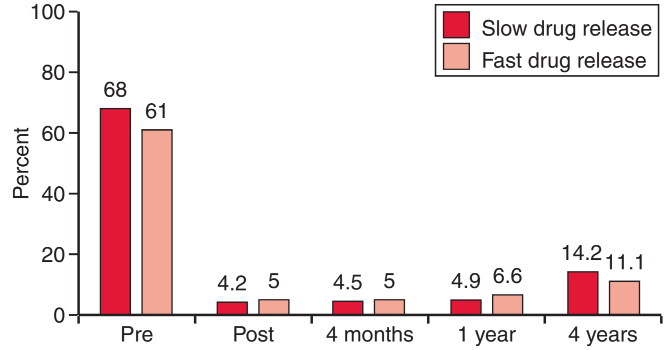
Type of Action	Name of Active Agent
Suppression of inflammation/immune response	Sirolimus (rapamycin) Zotarolimus Everolimus Tacrolimus Other analogs Paclitaxel Taxane Dexamethasone Methylprednisolone Other glucocorticoids Interferon-γ Mycophenolic acid Cyclosporine Tranilast Probucol Biorest Leflunomide
Suppression of cell proliferation (*also including smooth muscle cell migration)	Sirolimus* and analogs (as above)* Paclitaxel and analogs (as above) Actinomycin-D Methotrexate Angiopeptin Vincristine Mitomycin C-*myc* antisense oligopeptides Ribozymes
Suppression of extracellular matrix production (or modulation of its substance)	Batimastat Probucol C-proteinase inhibitors Prolyl-hydroxylase inhibitors
Enhancement of endothelialization and vascular healing	17 β-Estradiol, other gynecological hormones Nitric oxide donors Endothelial progenitor cell chemoattractants Vascular endothelial growth factor Statins

treatment with the eluted drug. This clinical observation also confirmed the negligible drug diffusion around the DES.

As a result of this observation, a new DES-deployment protocol was developed that included special attention to cover with a DES every arterial part that was injured during balloon predilation, and also to limit balloon predilation to the shortest balloon possible, avoid slippage during inflation, and even consider direct DES implantation without predilation. Indeed, the clinical results obtained in these subsequent studies[6-8] confirmed that with adherence to the outlined implantation protocol, both the within-stent and the peri-stent arterial segment develop minimal neointimal proliferation. Further support to full-segment coverage was provided by the widely documented very minor (actually almost zero in several analyses) increase in restenosis with increased length of DES implanted. The DES deployment technique was developed after the first sirolimus-eluting studies and has been recommended since that time for all DES systems.

Paclitaxel-Polymer-Based Eluting Stent

Both the slow- and moderate-release formulations of the paclitaxel DES system entered human trials (Table 7–3),[14-19] but the development process ultimately focused on the slow-release formulation DES, which was the second DES to be approved for human use, approximately 1 year after approval of the sirolimus-eluting stent. In all clinical trials with this stent, the deployment technique mandated complete injury segment coverage, as described earlier. In many clinical trials, the TAXUS-SR stent was shown to be safe and had significantly less restenosis and repeat revascularization rates than an identical bare-metal stent. Overall, the decrease in repeat revascularization has been the most consistent finding with the TAXUS stent compared with the identical bare-metal stent in the studies performed (3% to 6% repeat revascularization procedures, 5% to 8% restenosis with DES, both down from 11% to 12% and 24% to 27% with control stents, respectively).



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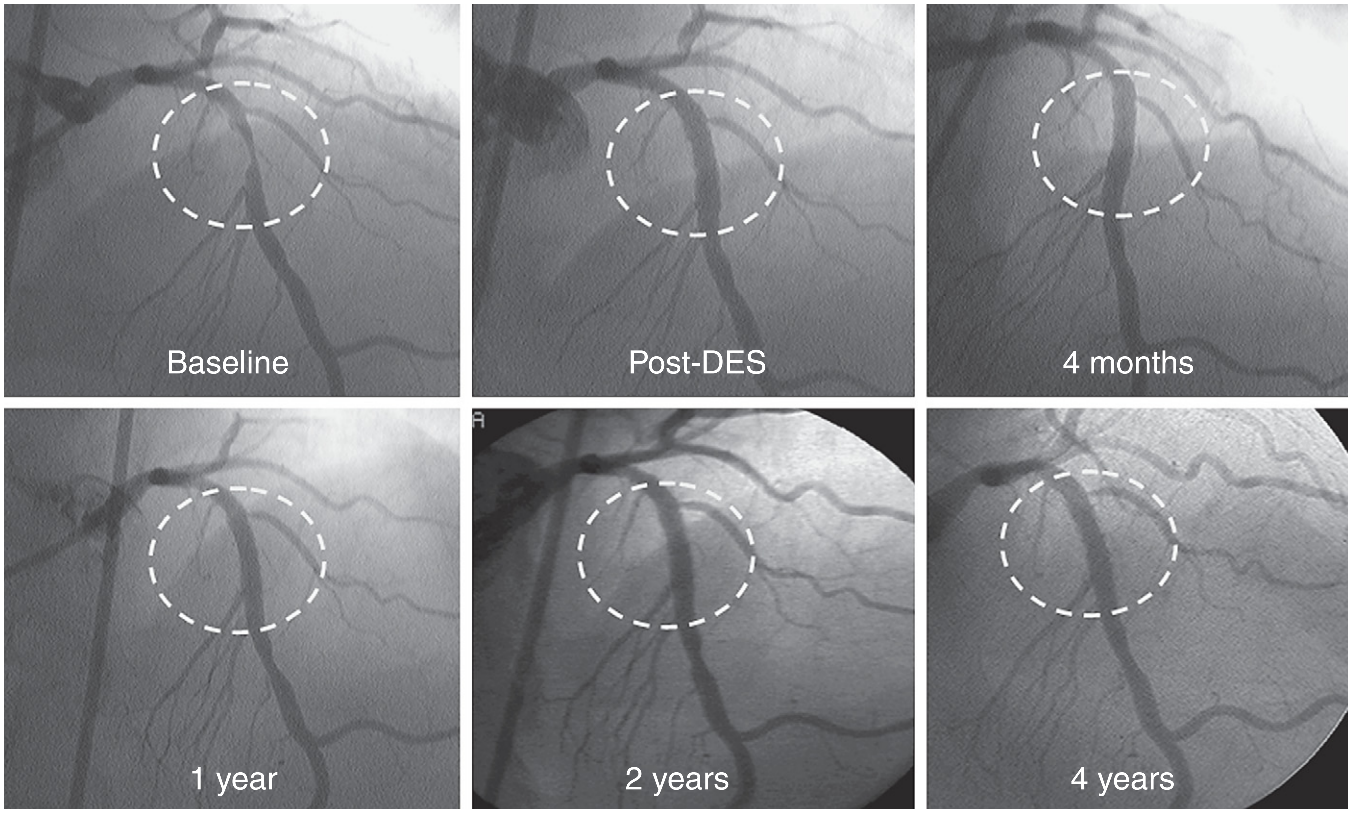

B

Figure 7–1 **A,** FIM 4-year results of diameter stenosis after sirolimus-eluting stent. **B,** Ultrasonographic example of 4-year arterial patency. FIM, first in man. (**A,** redrawn from Sousa JE, Costa MA, Abizaid A, et al: Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. Circulation 2005;111:2326-29.)

DES Comparison and Clinical Implication of Late Lumen Loss

Although both of the approved DES with sirolimus and paclitaxel elution have reduced the rate of binary restenosis (defined as >50% diameter stenosis at follow-up) and frequency of repeat procedures at the treated arterial segment, the late lumen loss values after each DES differed significantly (Table 7–4).[20-26] Late lumen loss with the sirolimus-eluting stent has been 0.1 mm to 0.2 mm, although it has never approached zero with the paclitaxel-eluting stent. With the paclitaxel DES, late lumen loss ranged from 0.25 mm to 0.55 mm; this value is still significantly lower than the values of 0.8 mm to 1.0 mm typically observed after bare-metal stent implantation.

This observation has been intriguing, because a higher late lumen loss was not clearly associated with increased restenosis and clinical events,[27] thereby implying two possibilities: (1) a yet unraveled difference in restenosis and repeat revascularization that could be uncovered through dedicated clinical trials; or (2) a uniform distribution of a thin neointimal tissue layer within the paclitaxel-eluting stent that could be either progressive over time and ultimately produce late restenosis and clinical events or stagnant over time—clinically harmless and even protective from unwanted DES contact with the arterial lumen.

A series of head-to-head trials of the two stent types were conducted in an attempt to investigate the first possibility listed in the preceding paragraph.[20-26,28] All of these studies unequivocally confirmed the significantly lower late lumen loss with the sirolimus-eluting stent. Regarding binary restenosis and recurrent clinical events, the results were not so clear. Although in every trial both restenosis and clinical event rates were arithmetically lower with the sirolimus-eluting stent, not all studies produced statistically significant event reductions. The strongest results were shown in a double-

Text continued on page 143.

Table 7–2 Sirolimus Drug-Eluting Stent (DES) Studies

Study Title (alphabetically)	Design	Inclusions	*N* (DES vs. Control)	Follow-Up (mos) Clinical/ Angiographic	Late Loss In-Stent (mm)	Restenosis in Segment (%)	TLR (%)	MACE (%)	Thrombosis (%)
DIABETES[9]	RCT vs. BMS	Elective procedure, de novo lesions in diabetic patients	75 vs. 74	12-9	0.08 vs. 0.66, $P < 0.0001$	7.7 vs. 33, $P < 0.0001$	7.5 vs. 31.3, $p < 0.0001$	11.3 vs. 36.3, $p < 0.0001$	0 in both groups
DIRECT[8]	Registry	Direct stent implantation technique in elective procedures; de novo lesions	225	6-6	0.18	6	NA TVF: 0.9	2.2	0.4
PRISON-II Presented by Suttorp MJ, TCT, Washington, DC, 2005	RCT vs. BMS	Elective procedure, de novo, single vessel, CTOs	100 vs. 100	6-6	–0.07 vs. 0.64, $P < 0.001$	11 vs. 41, $P < 0.0001$	4 vs. 19, $P = 0.01$	4 vs. 20, $P < 0.001$	2 vs. 0, P = NS
RAVEL[3]	RCT vs. BMS	Elective procedure, de novo, single vessel	120 vs. 118	12-6	–0.01 vs. 0.80, $P < 0.001$	0 vs. 26.6, $P < 0.001$	0. vs. 22.9, $P < 0.001$	5.8 vs. 28.8, $P < 0.001$ at 1 year, 22 vs. 35, $P = 0.04$ at 4 years	0 in both groups
RESEARCH[11]	DES Registry vs. historical BMS control	Unselected	508 vs. 450	12	NA	NA	NA TVR 3.7 vs. 10.9, $P < 0.0001$	9.7 vs. 14.8, $P = 0.008$	0.3 vs.1.6 $P = 0.1$
RESEARCH-ACS[12]	DES Registry vs. historical BMS control	Unstable angina or acute MI, de novo	198 vs. 301	12	NA	NA	NA TVR 4.1 vs. 10.9, $p = 0.0001$	9.1 vs. 14.9, $p = 0.002$	0.5 vs.1.7, $p = 0.41$
SIRIUS[5]	RCT vs. BMS	Stable or unstable angina, de novo, single vessel	533 vs. 525	9-8	0.17 vs. 1.00, $P < 0.001$	3.2 vs. 35.4, $P < 0.001$	4.1 vs. 16.6, $P < 0.001$	7.1% vs. 18.9	
E-SIRIUS[6]	RCT vs. BMS	Stable or unstable angina, de novo, single vessel	175 vs. 177	9-8	0.20 vs. 1.05, $P < 0.001$	5.9 vs. 42.3, $P < 0.0001$	5.1 vs. 21.7, $P < 0.0001$	8.1 vs. 22.8, $P < 0.0001$	1.1 vs. 0, P = NS

Table 7–2 Sirolimus Drug-Eluting Stent (DES) Studies—cont'd

Study Title (alphabetically)	Design	Inclusions	*N* (DES vs. Control)	Follow-Up (mos) Clinical/ Angiographic	Late Loss In-Stent (mm)	Restenosis in Segment (%)	TLR (%)	MACE (%)	Thrombosis (%)
C-SIRIUS[7]	RCT vs. BMS	Stable or unstable angina, de novo, long, small, single vessel	50 vs.50	9-8	0.12 vs. 0.79, $P < 0.001$	2.3 vs. 52.3, $P < 0.001$	4 vs. 18, $P = 0.05$	4 vs. 18, $P = 0.05$	2 vs. 2, $P = 1$
SES-SMART[13]	RCT vs. BMS	Stable angina, de novo, small, single vessel	129 vs. 128	8-8	0.16 vs. 0.69, $P < 0.001$	9.8 vs 53.1, $P < 0.001$	7 vs. 21.1 $P = 0.002$	9.3 vs. 31.3, $P < 0.001$	0.7 vs. 3.1, P = NS
SISR[75]	RCT vs. brachytherapy	In-stent restenosis, single vessel	259 vs. 125	9-8	0.27 vs. 0.33, $P = 0.33$	19.8 vs. 29.5, $P = 0.07$	8.5 vs. 19.2, $P = 0.004$	TVF: 12.4 vs. 21.6, $P = 0.02$	0.8 vs. 0, P = NS
SCANDSTENT[10]	RCT vs. BMS	Stable or unstable angina, complex lesions (occluded, bifurcational, ostial, or angulated)	163 vs. 159	12-9	0.04 vs. 0.94, $P < 0.001$	2 vs. 31.9, $P < 0.0001$	2.4 vs. 29.6, $P < 0.001$	3.1 vs. 31.2, $P < 0.001$	30 days: 0.6 vs. 3.1
TROPICAL Presented by Neumann FJ, EURO-PCR, Paris, France, 2004	Registry	In-stent restenosis	155	6-6	0.08	9.7	2.5	3.7	0.6

BMS, bare metal stent; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not available; RCT, randomized clinical trial; TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization.

Table 7–3 Paclitaxel Drug-Eluting Stent (DES) Studies

Study Title (alphabetically)	Inclusions	*N* (DES vs. Control)	Follow-Up (months) Clinical/ Angiographic	Late Loss In-Stent (mm)	Restenosis In-Segment (%)	TLR (%)	MACE (%)	Thrombosis (%)
TAXUS I[14] (NIR stent, slow drug release)	Stable angina, de novo simple lesions	31 vs. 30	12-6	0.36 vs. 0.71, $P < 0.01$	0 vs. 10.0, P = NS	3.3 vs. 10.0, P = NS	3.3 vs. 10.0	0 in both groups
TAXUS II[15] cohort-1 (NIR stent, slow drug release)	Stable angina, de novo simple lesions	131 vs. 136	12-6	0.31 vs. 0.78, $P < 0.01$	5.5 vs. 20.1, $P < 0.05$	4.7 vs. 12.9, $P < 0.05$	10.9 vs. 22.0, $P < 0.05$	1.7 vs. 0
TAXUS II[15] cohort-2 (NIR stent, moderate drug release)	Stable angina, de novo simple lesions	134 vs. 135	12-6	0.30 vs. 0.78, $P < 0.01$	8.6 vs. 23.8, $P < 0.05$	3.8 vs. 16.0, $P < 0.05$	9.9 vs. 21.4, $P < 0.05$	0.7 vs. 0
TAXUS III[16] (NIR stent, slow drug release)	In-stent restenosis registry	28	12	0.56	16.0	21.5	28.6	0
TAXUS IV[17,18] (Express stent, slow drug release)	Stable or unstable angina, de novo lesions, high complexity	662 vs. 652	9-9	0.39 vs. 0.92	7.9 vs. 26.6, $P < 0.05$	3.0 vs. 11.3, $P < 0.05$	8.5 vs. 15.0, $P < 0.05$	0.6 vs. 0.8
TAXUS-V (Express stent, slow drug release) Presented by Stone GW at ACCIS, Orlando, FL, 2005	Stable or unstable angina, de novo complex lesions; multiple stents allowed	577 vs. 579	9-8	0.49 vs. 0.90	18.9 vs. 33.9, $P < 0.01$	8.6 vs. 18.9, $P < 0.01$	15.0 vs. 21.2, $P < 0.001$	0.7 in both groups
TAXUS VI[19] (Express stent, moderate drug release)	Stable or unstable angina, de novo lesions, high complexity	217 vs. 220	12-9	0.39 vs. 0.99	9.1 vs. 32.9, $P < 0.05$	6.8 vs. 18.9, $P < 0.05$	16.4 vs. 22.5, P = NS	1.3 vs. 0.5

See Table 7–2 for acronym definitions.

Table 7–4 Cypher versus TAXUS Studies

Study Title (alphabetically)	Inclusions	*N* (Cypher vs. Taxus)	Follow-Up (months) Clinical/ Angiographic	Late Loss In-Stent (mm)	Restenosis In-Segment (%)	TLR (%)	MACE (%)	Thrombosis (%)
BASKET[20]	Stable or unstable angina, native de novo lesions	264 vs. 281 vs. 281 with cobalt chromium BMS	6	NA	NA	NA TVR was 3 vs. 6 vs. 7.8, *P* = NS between DES, *P* = 0.08 for DES vs. BMS	5.7 vs. 8.5 vs. 12.1, *P* = NS between DES, *P* = 0.02 for DES vs. BMS	1% in all groups
CORPAL[21]	Stable or unstable angina, native de novo lesions	331 vs. 321	6		12.4 vs. 18.6, *P* = NS	5.7 vs. 9.0, *P* = NS		0.6 vs 0
ISAR-DIABETES[23]	Diabetic patients with stable or unstable angina, de novo lesions in a single vessel	125 vs. 125	6	0.19 vs. 0.46, *P* = 0.001 0.43 vs. 0.67 in-segment *P* = 0.002	6.9 vs. 16.5, *P* = 0.03	6.4 vs. 12.0, *P* = 0.13	NA 9-month death: 3.2 vs. 4.8, *P* = 0.52	30 days: 0 vs 0.8
ISAR-DESIRE[22]	In-stent restenosis, single vessel	100 vs. 100 vs. 100 with balloon angioplasty alone	12	0.21 vs. 0.48, *P* = 0.006 0.45 vs. 0.66 in-segment *P* < 0.02	14 vs. 22 vs. 45, *P* = 0.19 between DES, *P* < 0.001 vs. balloon angioplasty for both DES	NA TVR was 8 vs. 19 vs. 33, *P* = 0.02 between DES, *P* < 0.001 vs. balloon angioplasty for both DES	NA	NA
REALITY (Morice MC, presented at ACCIS, Orlando, FL, 2005)	Stable or unstable angina, 1 or 2 de novo lesions	684 vs. 669	8	0.09 vs. 0.31, *P* < 0.001	9.6 vs. 11.1, *P* = 0.32	5.0 vs. 5.4, *P* = 0.81	9.2 vs. 10.6, *P* = 0.41	0.4 vs. 1.8

continued

Table 7–4 Cypher versus TAXUS Studies—cont'd

Study Title (alphabetically)	Inclusions	*N* (Cypher vs. Taxus)	Follow-Up (months) Clinical/ Angiographic	Late Loss In-Stent (mm)	Restenosis In-Segment (%)	TLR (%)	MACE (%)	Thrombosis (%)
SIRTAX[24]	All pts (real world), de novo lesions	503 vs. 509	9	0.13 vs. 0.25, $P < 0.001$ 0.19 vs. 0.32 in-segment $p < 0.001$	6.7 vs. 11.9, $P = 0.02$	4.8 vs. 8.3, $P = 0.025$	6.2 vs. 10.8, $P = 0.009$	2.0 vs. 1.6
TAXI[25]	All patients with stable or unstable angina and a de novo lesion	102 vs. 100	12	NA	3 vs. 6, $P = 0.5$	3 vs. 1, P = NS	8 vs. 7, P = NS	1 vs. 0
T-SEARCH[26] Cypher group is historical control	All patients ("real world"), de novo lesions, single center, nonrandomized design	508 vs. 576	12	NA	NA	NA TVR was 3.7 vs. 5.4, $P = 0.$	10.5 vs. 13.9, $P = 0.1$	

See Table 7–2 for acronym definitions.

center study that included a largely unselected population (elective, stable/unstable angina and acute myocardial infarction with few lesion restrictions)[24]; whereas the less significant results occurred in a multicenter trial on less clinical acuity and lesion complexity (Marie-Claude Morice, oral presentation, ACCIS, March 6, 2005, Orlando, FL). Whether these facts truly support option 1—described earlier—remains to be verified in larger trials.

Additionally, in the absence of large studies with long-term systematic and periodic angiographic follow-ups, it is also impossible to render a definitive opinion regarding the progress of the late lumen loss disparity between the two DES types. The incidence of clinical events related to the target vessel during the long-term follow-up phase (beyond the primary endpoint assessment) of all the DES trials will be used as an important clinical surrogate when it becomes available.

Zotarolimus-Eluting Stents

The third DES approved for human use in Europe is the phosphorylcholine-encapsulated zotarolimus (also known as ABT-578)-eluting cobalt alloy stent (Endeavor Stent, Medtronic Vascular, Santa Rosa, CA).

Clinical results with the zotarolimus stent (Table 7–5)[29,30] have indicated (1) favorable safety with very low rates of stent thrombosis; (2) lower restenosis and clinically driven target lesion reintervention than an identical bare-metal stent; (3) significantly higher late lumen loss (0.5 to 0.6 mm) than the sirolimus-eluting stent; (4) similar rate of target lesion reintervention to the sirolimus-eluting stent; and (5) improved technical success (likely because of improved stent delivery) and lower periprocedural events (possibly related to technically easier procedures with a more deliverable stent, less side-branch compromise, or both). Large ongoing trials are investigating its differences to the paclitaxel-polymer-based eluting stent and its clinical results when implanted in higher-risk patients and lesion subsets.

The observations made with this DES emphasize the importance of clarifying the clinical implications of late lumen loss after DES placement.[27] The described differences between the sirolimus and the paclitaxel-approved DES systems appear to be similarly reproduced by a new DES that uses a sirolimus analog. Therefore, the profound suppression of late loss with the sirolimus-eluting stent may be particularly related to the specific compound (as opposed to its chemical class), or to a very unique and highly important combination of polymer structure and drug-delivery kinetics. It is noteworthy that a DES with late loss of 0.6 mm still produces important reductions in restenosis and recurrent events compared with a bare-metal stent with late loss of 0.5 mm to 0.6 mm at the same time that its clinical effect is not clearly inferior to another DES that has late loss of approximately 0.1 to 0.2 mm. Painstaking mathematical modeling after pooling angiographic and clinical data from all DES studies, as well as dedicated studies with periodic angiographic follow-up, may shed light on this phenomenon. Noninvasive coronary imaging with computerized tomography with enhanced in-stent imaging capability may enable the conduct of studies with serial coronary angiography and clinical follow-up blinded to the angiographic results.

Another zotarolimus-eluting stent composed of tantalum and stainless steel in a tri-layer design and encapsulated with a modified phosphorylcholine coating has been used in clinical trials—those results are pending.[1]

CLINICAL USE OF DES IN DIFFERENT PATIENT AND CLINICAL SUBSETS

DES have been mainly used in selected patient and lesion subsets before regulatory approval, which is granted for a rather narrow indication—one that does not represent more than 10% of lesions treated in contemporary interventional cardiology. Therefore, gradual accumulation of “real-world” results in unselected patient and lesion types has been historically viewed to be very important for the expansion of clinical applications of the new interventional devices. Such data have been particularly important in the DES area because of the very high expectations of interventional cardiologists from the remarkable safety and efficacy of the DES treatment shown in the preapproval trials.[1]

In general, every interventional device has somewhat less favorable results when applied in the “real-world” depending on the complexity of the device, the learning curve for its use, and the frequency of its use. DES have been used with high (and increasing) frequency and have a brief (although finite) learning curve. We have already described the quick revision of the DES implantation technique after the first large sirolimus-eluting stent multicenter trial. Had this issue not been resolved so fast, a series of prospective DES studies and many “real-world” series would have been plagued by this problem.

The performance of DES in the “real-world” has been quite satisfactory, although not as dramatically effective as in the preapproval randomized trials. A detailed analysis of DES performance within each and every patient and lesion subset is beyond the scope of this chapter, but DES patient subsets with the highest clinical importance or those that are particularly problematic compared with bare-metal stent treatment will be highlighted.

High-Risk Lesion Subsets

Lesion subsets that have been difficult to treat successfully with metal stents are long lesions,[6,31] ostial lesions,[32-34] and those in small vessels.[26,35,36] Treatment of any of these lesion types with DES has been clearly superior to bare-metal stents. In treating long lesions, the operator should provide full lesion coverage because the “restenosis penalty” is no longer proportional to stent length when a DES is used.[37-40] Particularly in vessels with a small reference lumen diameter, DES with very little late lumen loss may be more useful because late loss may correlate more tightly with binary restenosis in small vessels. Complete apposition and expansion are always important for DES implantation but are of particular importance in ostial lesions owing to the greater chance of proximal-distal vessel size disparity, eccentricity, and negative remodeling that may resist expansion.[41,42] Routine postdilation with appropriately sized noncompliant balloons is recommended in such cases.

DES implantation in diffuse disease should not be expected to yield as favorable results as in discrete lesions. Although there is not a large restenosis penalty for use of long stents, the risk of complications is high if DES is not implanted from “healthy to healthy” arterial segments. In

Table 7–5 Zotarolimus Drug-Eluting Stent (DES) Studies

Study Title	Pts	*N* (DES vs. Control)	Follow-Up (months) Clinical/ Angiographic	Late Loss In-Stent (mm)	Restenosis In-Segment (%)	TLR (%)	MACE (%)	Thrombosis (%)
Endeavor I (registry)[29]	Stable angina, single, de novo lesion	100	12-12	0.33 at 3 months 0.61 at 1 year	5%	2%	2%	1%
Endeavor II (vs. BMS)[30]	Stable angina, single, de novo lesion; longer lesions/stents included	598 vs. 599	9-8	0.61 vs. 1.03, $P < 0.001$	9.5 vs. 33.5, $p < 0.001$	4.6 vs. 11.8, $P < 0.001$	7.3 vs. 14.4, $P < 0.001$	0.5 vs. 1.2, P = NS
Endeavor II (registry)[30]	Same as Endeavor II	300	9-8	0.56	14.2	4.8	13.1	0
Endeavor III vs. Cypher Kandzari DE, Leon MB: Oral presentation at TCT-2005, Washington, DC	Stable angina, single, de novo lesion	327 vs.109 with Cypher	9	0.60 vs. 0.15, $P < 0.001$	11.7 vs. 4.3, $P = 0.04$	6.3 vs. 3.5, P = NS	7.6 vs. 7.1, P = NS	0

See Table 7–2 for acronym definitions.

diffuse disease, it may be impossible to identify the healthiest area. The occurrence of diffuse disease in small vessels typically places such patients at high risk for any revascularization procedure (DES or bypass surgery). The operator should weigh selective DES implantation at the tightest spots versus the "full-metal jacket" approach versus bypass surgery versus medical therapy in a patient with diffuse disease.[43-45]

Treatment of saphenous vein grafts has classically been a problematic area because, by definition, these patients have already failed a bypass operation and the vein grafts are particularly prone to distal embolization and other procedural complications.[46,47] Most DES are not available in sizes greater than 3.5 mm in diameter. Even with aggressive postdilation, the 3.5 mm DES cannot reliably expand more than 4.5 mm. The large size of vein grafts may not allow implantation of DES, or may lead to distal embolization during the high-pressure postdilation. Results from DES registries indicate that the clinical recurrence after DES implantation in saphenous vein grafts is markedly lower than expected with bare-metal stents; hence, DES can be used in vein grafts provided that the clinician has taken into account the technical limitations just discussed.[48-50]

Both single center registries[51-53] and a randomized study (Maarten J. Suttorp, oral presentation of PRISON-II study at TCT, October 17-21, 2005; Washington, DC) have indicated marked restenosis reduction with DES compared with bare-metal stents in chronic total occlusions. Again, this lesion subtype had been related to increased restenosis and reocclusion after angioplasty, with modest improvement with bare-metal stents. Advances in wire technique and technology that enable greater success in crossing the occlusion have energized the attention to this lesion type.[54,55]

Bifurcation and Left Main Coronary Artery Lesions

A frontier not explored extensively with bare-metal stents owing to high restenosis and recurrent clinical events includes bifurcation and left main coronary artery lesions. The initial enthusiasm with DES in bifurcation lesions was concurrent with the development of the "crush" technique for deployment of DES in both the parent and the daughter vessels.[56,57] Despite encouraging early results, routine deployment of two DES in bifurcations is currently not recommended, because the restenosis in the daughter vessel has been as high as 20%, along with a very low restenosis in the main vessel (Fig. 7–2).[58] A provisional stent approach should be used, with the decision to deploy a DES also in the daughter vessel in case of a persistent high-grade stenosis dissection or a moderate stenosis in the presence of an unfavorable take-off angle after balloon predilation.[56]

A relation between bare-metal stent restenosis and sudden cardiac death had been raised in certain left main series and never definitively proved or negated.[1] Therefore, the emergence of a very low restenosis rate with DES reintroduced the concept of left main stenting, especially because its large vessel size would place the left main coronary artery in the most favorable lesion subset. Indeed, initially encouraging results have been obtained with restenosis <10%.[59] The outcome is dependent on the lesion location: an ostial or main body lesion that can be covered by a DES without any involvement of the left main bifurcation is considered the most favorable lesion type. Involvement of the bifurcation introduces several technical issues depending on the exact regional anatomy.[60-62] In such cases, the techniques vary significantly worldwide: single DES into the proximal left anterior descending artery with "jailing" of the circumflex artery is mostly followed in Asia, the T-stent or simultaneous "kissing" stent deployment has been considered in Europe and the United States according to treatment of other lesions within the left anterior descending and circumflex arteries. A dedicated international left main DES (with the sirolimus-eluting stent) versus bypass surgery trial is underway. At this point, routine angiographic follow-up should be recommended at 4 to 6 months and 12 to 14 months postprocedure for every patient who receives a left main DES. In this patient subset, preoperative clearance for high-risk noncardiac surgery at any later time should reasonably include repeat coronary angiography.

Multivessel Disease and Diabetes

The most interesting and controversial patient and lesion subtypes include the use of DES for diabetic patients and multivessel coronary artery disease. The initial multicenter results of DES use in diabetic patients (under 25% of any trial had diabetes) were controversial,[5,6,18] but subsequent randomized trials have actually shown lower restenosis and clinical events with the sirolimus-eluting stent compared with bare-metal[63] and paclitaxel-eluting stents.[23] The comparative DES study results should be considered preliminary, and verification in another study should be sought; registry data are also generated.

The use of DES in multivessel disease (25% diabetics were included in the cohort) was studied in the Arterial Revascularization Trial Study part II (Fig. 7–3).[64] In this study, identical inclusion and exclusion criteria to the ARTS-I trial[65] were used to develop a study group treated with multiple sirolimus-eluting stents. This DES cohort included more diabetics (25%), longer lesions and stents, and more lesions and stents per patient compared with the ARTS-I trial. Compared with the ARTS-I bare-metal stent group, lower stent thrombosis and periprocedural events were documented (the use of glycoprotein IIb/IIIa inhibitors was also significantly higher in the DES group) and superior long-term major adverse cardiovascular event rate was observed. The long-term results available thus far were superior even to those documented in the bypass surgery group of the ARTS-I trial according to Bayesian analysis.[64] A 3- to 5-year follow-up is expected.

These results have provided the rationale for two ongoing prospective trials. One study [SYNergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery (SYNTAX)] compares the implantation of TAXUS-SR with bypass surgery in patients with multivessel disease (also allowing inclusion of patients with stenotic left main lesions) with a 1-year cardiovascular event rate primary endpoint and 5-year subsequent follow-up. The other study (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease [FREEDOM]) compares the implantation of any approved DES (either sirolimus-eluting or paclitaxel-polymer-based-eluting stent up to now) with bypass surgery in patients with diabetes mellitus and multivessel coronary artery disease (excluding left main); there is a 3-year primary endpoint of death, nonfatal myocardial infarction, or stroke.

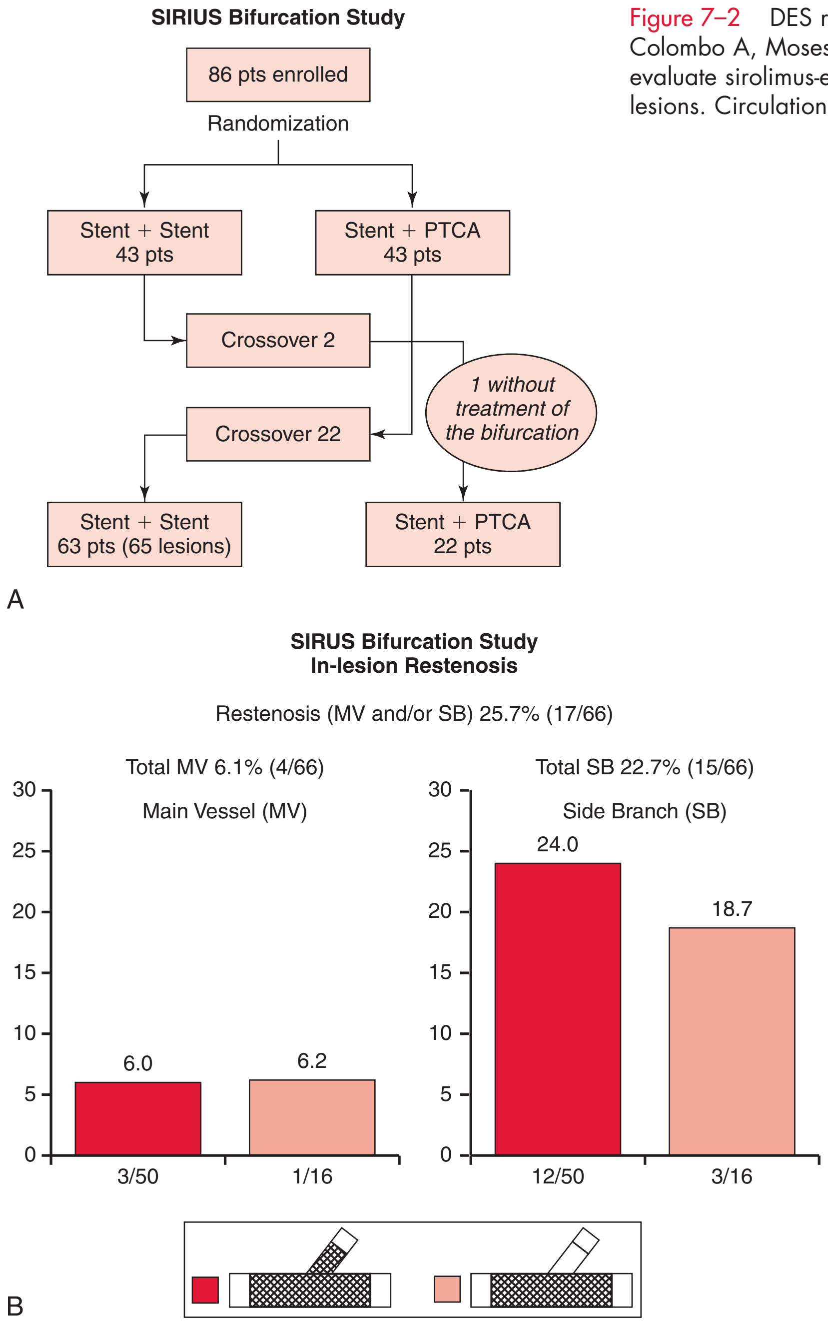

Figure 7–2 DES results in bifurcation lesions. (Redrawn from Colombo A, Moses JW, Morice M-C, et al: Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation 2004;109[10]:1244-9.)

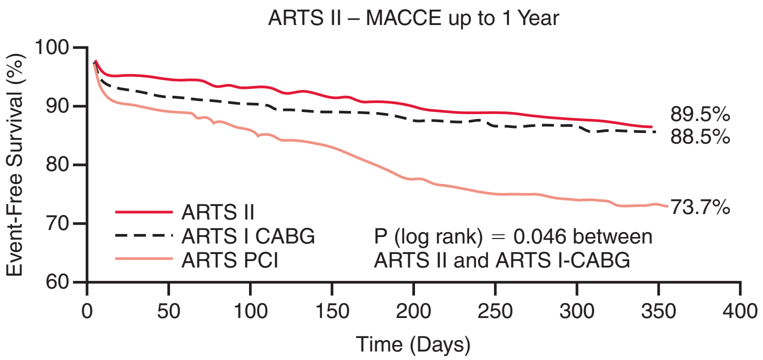

Figure 7–3 Results of the ARTS-II trial. (Redrawn from Serruys PW, Morice M-C: Arterial Revascularisation Therapies Study. II. Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. Eurointervention 2005;1:147-56.)

Acute Coronary Syndromes

Owing to initial prothrombotic concerns with use of DES, clinical results of DES in patients with an acute coronary syndrome (ACS) became critically important. Several results to date have indicated that DES implantation in ACS patients is safe and effective.[12,66,67] Particularly for unstable angina, there is no controversy and the use of DES is well accepted. Some controversy still exists regarding DES use in the acute phase of ST-segment elevation myocardial infarction; this has been sparked mostly by sporadic, single-center experiences rather than by clinical study results.[68,69] Given that many factors can potentially affect the occurrence of stent thrombosis[70] in primary or rescue angioplasty, and given that there are fewer patients with myocardial infarction than with unstable angina, this controversy is to a certain extent expected because of the event rate variability from center to center. In several "real-world" registries, and in a large, double-center European study comparing two DES types in unselected patients including ACS, no adverse events were noted in the myocardial infarction subset.[24,69,71-73] A large, ongoing multicenter trial of primary angioplasty in acute myocardial infarction randomizes the paclitaxel-polymer-based-eluting stent to identical bare-metal stent and will provide invaluable clinical insights.

IN-STENT RESTENOSIS

Vascular Brachytherapy

The only device formally approved for treatment of bare-metal in-stent restenosis is vascular brachytherapy. However, its complex multidisciplinary set-up and the disappointing late recurrence rates[74] in comparison with the ease of use and favorable results of DES have contributed to the world-wide abandonment of brachytherapy. Furthermore, randomized trial results have shown superior results with DES than with brachytherapy for bare-metal stent restenosis (see Table 7–2).[75]

A compassionate use registry of sirolimus-eluting stent included only "no-option" patients.[76-78] The subset of patients who had failed brachytherapy (administered for prior bare-metal stent restenosis) and were subsequently treated with DES had significantly worse outcomes (>25% major adverse event rate) than the remaining high-risk patients. Based on these results, treatment with DES after brachytherapy is generally discouraged; it could be considered only for focal recurrence or if the possibility of bypass surgery does not exist and periodic angiographic follow-up should be recommended. Because vascular brachytherapy is no longer used, this problem will be seen progressively less frequently.[79]

DES for Bare-metal Stent Restenosis

Use of DES for in-stent restenosis as first-line therapy (i.e., without prior brachytherapy) has been studied in registries, subgroups of major trials, and dedicated randomized studies.[16,22,80-82] The results indicated a favorable efficacy and safety; however, there are some caveats that should be highlighted.

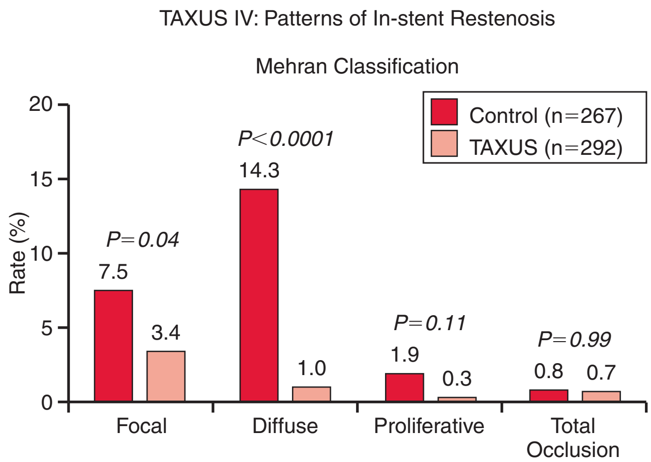

Figure 7–4 Not only do DES reduce restenosis, but they also shift the distribution of recurrent in-stent restenosis pattern to predominantly focal presentation. (Redrawn from Iakovou I, Schmidt T, Ge L, et al: Angiographic patterns of restenosis after paclitaxel-eluting stent implantation. J Am Coll Cardiol 2005;45[5]:805-6.)

In treating in-stent restenosis, it is important to understand its mechanism,[83] stent under-expansion, and other local mechanical complications. Edge restenosis versus excessive neointimal proliferation within a well-expanded stent can be differentiated with intravascular ultrasound imaging. Patterns of in-stent restenosis are shown in Figure 7–4.

When necessary, optimization of stent expansion with high-pressure balloon inflation should be undertaken first. If stent expansion does not improve, further treatment with DES or bare-metal stent is not indicated and could be harmful owing to the possibility of thrombosis at the site of spot of stent underexpansion. In such unusual, high-risk cases the operator should evaluate (depending on lesion location, vessel size, and overall patient condition) the options of balloon angioplasty alone, bypass surgery, or advanced interventional techniques with rotational ablation of the old stent struts and the rigid-calcified plaque behind them to allow appropriate expansion of the new stent.

If restenosis occurs at a stent edge or when the original stent is well expanded (or after its expansion is successfully improved with high-pressure balloon dilation), treatment with DES is currently considered the treatment of choice with complete lesion segment coverage. Lesion subsets that are specifically problematic when restenosed are the bifurcation lesions originally treated with two stents. In such cases, the metallic configuration at the bifurcation may be precluding any stent advancement into the side branch and the treatment with DES may not be as helpful owing to potential local underexpansion due to the amount and configuration of "old" metallic stents.

DES Restenosis

Although rare, restenosis still occurs after DES implantation and warrants specific management plans. An important observation from randomized DES trials is that in the restenosed lesions, the lesion length is significantly shorter after DES than after bare-metal stent implantation.[84-86]

Accordingly, DES restenosis is mostly focal (>85% of cases), whereas bare-metal restenosis is mostly diffuse (>65% of cases). Because focal in-stent restenosis has a far better response to subsequent treatment and prognosis than do diffuse, proliferative and occlusive patterns, DES restenosis appears more favorable than bare-metal stent restenosis.[69]

Intravascular ultrasound imaging can help identify reasons for DES restenosis. Attention should be paid to the same issues as just described regarding original stent underexpansion.[87] Other morphological issues that may be revealed with such imaging are (1) stent malapposition,[88] which should be corrected when associated with restenosis; (2) stent fracture, which may occur infrequently at bend points or at stent overlap that may require additional DES implantation[89]; (3) incomplete lesion coverage that manifests as edge restenosis[90] while the entire original stent is actually free of intimal hyperplasia; and (4) a gap between two DES that requires coverage.

Treatment of DES restenosis should be guided by an understanding of the local morphology as outlined, and in general includes implantation of new DES of the same type in cases of focal restenosis, edge restenosis (with previously incomplete lesion coverage), stent gap, or fracture. Typically, the new DES should be as short as possible but still respect the rule of complete segment coverage. In restenotic cases within the main stent body due to focal underexpansion or intimal hyperplasia, local treatment with a noncompliant (high-pressure) balloon, or preferably with a cutting balloon, could be attempted and implantation of a new DES could be reserved for failures of this approach.[91]

In cases of diffuse in-stent restenosis lesions that can be clearly covered by additional DES (i.e., obvious proximal and distal "healthy" landing zone), use of an alternative DES type can be considered[92] if intimal hyperplasia is the dominant mechanism. This may be helpful because a different antiproliferative drug would be eluted locally (at a site that demonstrated "resistance" to the originally eluted drug), but the lack of well-documented benefits and risks of this approach need to be clearly understood. In our practice, we have not noticed obvious early or late adverse events.

Intravascular ultrasound imaging has indicated that there is an adverse interaction between small final stent cross-sectional area at the time of original DES implantation and stent length, with the highest restenosis chance when the area is under 5.5 cm^2 and the length longer than 40 mm (17% with both factors present versus 0.4% with both factors absent).[93] Therefore, clinicians should pay detailed attention to DES expansion when restenosis occurs in long DES.

High-risk DES restenosis cases necessitating the consideration of bypass surgery include complex configuration of multiple restenosed DES (especially in bifurcations), many DES layers due to repeat restenosis, or any involvement of the left main bifurcation.

DES THROMBOSIS

DES thrombosis has been highlighted in various forms since the introduction of DES because of its severity and despite its rarity.[93-98] Local thrombogenicity may arise from several factors including metallic stent type configuration (wall coverage, tissue prolapse , side-branch compromise), polymer, type of eluted agent and local dosage, antithrombotic therapy, and patient-lesion characteristics. A specific underlying mechanism pertinent for DES is the time to achievement of complete endothelialization, which is extremely difficult to assess in vivo.[99] To account for this factor, DES implantation is performed with the recommendation to follow an extended period of dual antiplatelet therapy.

Initial clusters of subacute thrombosis were documented sporadically shortly after introduction of DES in clinical practice but this problem reduced in frequency with additional experience and adoption of complete disease segment coverage with the DES, and detailed attention to apposition, expansion, and overlap zones. No DES randomized trial documented excess stent thrombosis compared with control bare-metal stent.

Interestingly, certain studies found an excess (with weak statistical significance) of thrombosis with the paclitaxel polymer-based DES compared with the sirolimus-eluting DES.[28,100] Clearly, the very low frequency of thrombotic events has made firm conclusions very difficult to achieve, and the design of a definitive trial would require an extremely large number of patients. Similarly, an initial report of acute intraprocedure thrombosis during DES implantation[101] has not been corroborated by other reports, and this problem is no longer considered a significant issue.

A large "real-world" registry focused on patient and lesion characteristics that may predispose to DES thrombosis, with premature interruption of dual antiplatelet therapy being by far the leading such factor (29%); other important factors include previous brachytherapy (see earlier), chronic renal failure, bifurcations, unprotected left main coronary artery, diabetes, and acute coronary syndrome (with descending rates of 8.7% to 1.3%).[100]

At the i2/ACC-2006 conference (March 7-11, 2006, Atlanta, GA), two randomized studies from Europe addressed the issue of DES versus bare metal stenting in acute myocardial infarction (Christian Spaulding and Marits Dirksen presenters). The stent thrombosis rates were similar between DES and control, but one of the studies reported those rates to be 3% to 4%, which is higher than expected. This raises again the possibility of an underestimation of thrombosis rates after bare metal stenting because of the familiarity with these devices and the rarity of the events. Nonetheless, this underlies the significance of adjunctive pharmacologic therapy for high-risk stent procedures.

The time course of stent thrombosis after DES appears to be more extended than after bare-metal stenting. Following bare-metal stenting, a steep decrease was noted after 2 weeks and a near-elimination after 1 month, although sporadic cases long after implantation still existed.[1] Following DES, the first month is still an important time point, with a decreased incidence between 1 and 3 months, a finite incidence between 3 and 6 months (<1% over 3 months), and sporadic cases thereafter (<1%). Because the incidence of DES thrombosis is similar overall to or just marginally higher than that seen with bare-metal stent (by 0.5%), these time-related fluctuations are quite difficult to establish definitively as unequivocal facts. It is difficult to meaningfully analyze the precise causes and risk factors of each individual case. In most instances, multiple factors contribute including influences from the DES device, patient, lesion, and pharmacologic therapy.[1,100]

With more time elapsed since DES approval, there is extended long-term follow-up available that has led to the

observation of occasional, unusual occurrence of late (>1 year after implantation) DES thrombosis, in association with the absence of dual antiplatelet therapy or a noncardiac thrombogenic stimulus.[100,102,103] Again, the rarity of such events and the absence of adequate control groups provide unsurpassable methodological limitations that preclude a definitive ruling. However, the intrinsic theoretical DES thrombogenicity and delayed endothelialization, both of which may have varying clinical significance in different patients, lesions, and clinical situations, necessitate the formulation of certain "expert" recommendations that will be discussed later in the adjunctive pharmacology section.

Treatment of DES thrombosis is based on previous knowledge from bare-metal stent thrombosis. Immediate fibrinolytic therapy (if an acute ST-elevation myocardial infarction occurs at a hospital without interventional cardiology services or the ability to transfer promptly), or therapy with heparin and glycoprotein IIb/IIIa inhibitor followed by immediate angioplasty are generally indicated depending on the location of the original stent and other patient-lesion characteristics. Intravascular ultrasound imaging can offer valuable information regarding stent malapposition, underexpansion, dissection, or incomplete lesion coverage with plaque rupture at an adjacent nonstented spot. Any of these situations warrants specific interventional approaches, and if they are not addressed properly, they will lead to further thrombotic complications. Overall thrombus load may selectively necessitate the use of thrombectomy devices. These devices should not be used routinely and without angiographic thrombus. Aortocoronary bypass surgery should be an option after the acute myocardial infarction phase in cases with suboptimal interventional results at the thrombosed segment in the presence of viable myocardium and in cases with several other unrevascularized territories.

ADJUNCTIVE PHARMACOLOGIC THERAPY

This section will address the pharmacologic therapy issues during DES implantation in various clinical and anatomic scenarios. The selection of the type of stent for any of these situations is beyond the scope of this chapter. This should not be interpreted as if DES were routinely indicated in all patients who belong in the clinical situations discussed hereafter.

Preprocedure and intraprocedural pharmacologic therapy during DES implantation should follow the recommendations for bare-metal stent implantation.[104] Early preprocedure establishment of aspirin and clopidogrel therapy is critical (at least 3 days in advance whenever possible), and a loading dose of clopidogrel (600 mg on the day of the procedure or 300 mg on the day before) should be given (Figs. 7–5 through 7–7). Heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors should be used intraprocedurally,[104] with the understanding that limited data exist on the use of these agents with DES. In a largely unselected prospective DES registry with 1-month follow-up, bivalirudin showed a favorable safety profile[105]; use of this agent should be

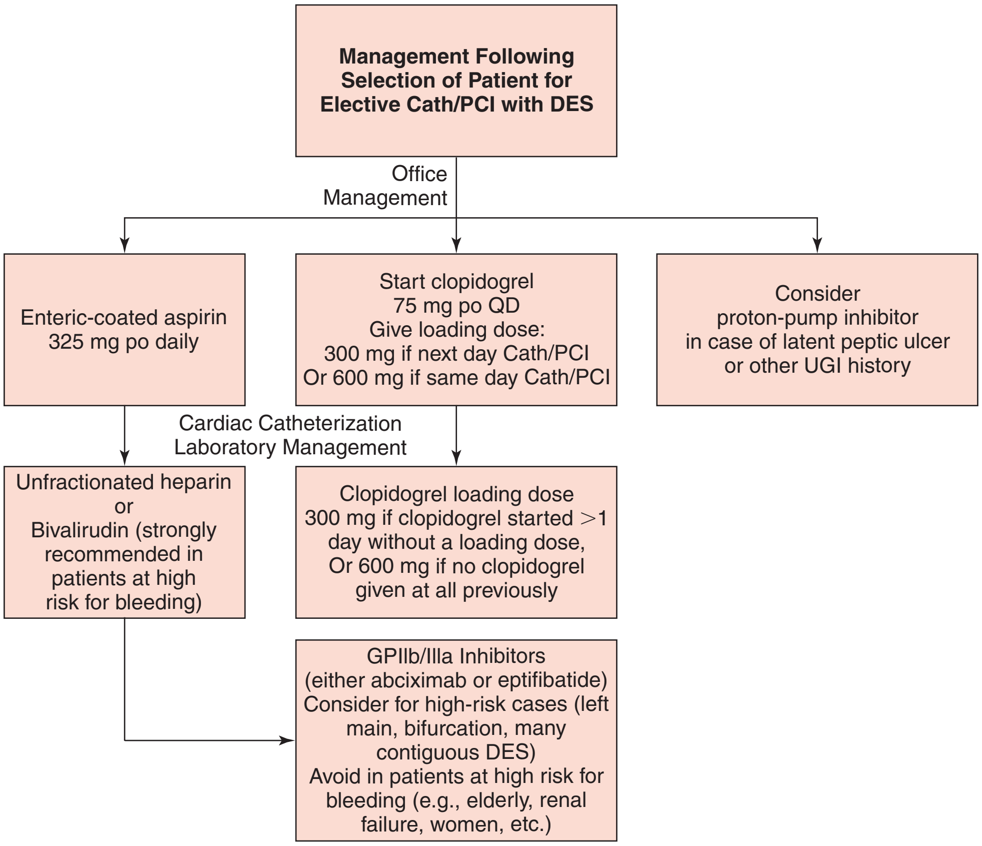

Figure 7–5 Algorithm for medical management of an elective patient referred for coronary angiography and possible percutaneous intervention (PCI) with a drug-eluting stent (DES). PO, by mouth; QD, every day; UFH, unfractionated heparin; UGI, upper gastrointestinal.

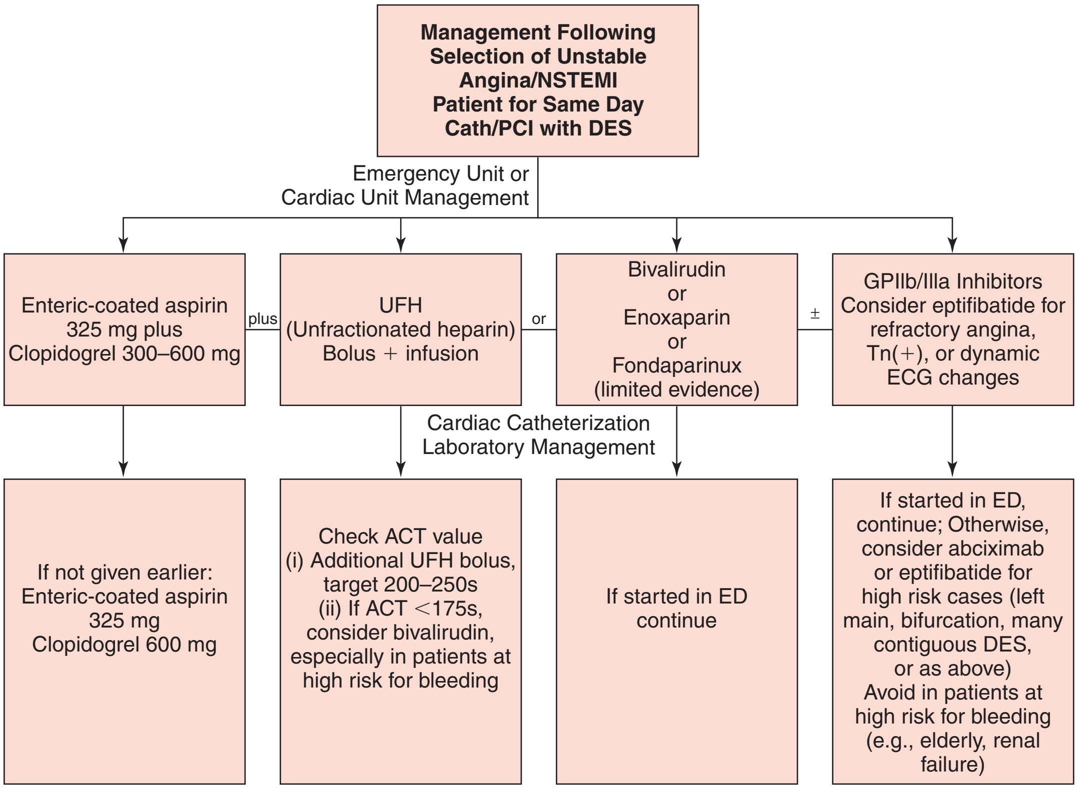

Figure 7–6 Algorithm for medical management of a patient with unstable angina or non-ST-elevation myocardial infarction (NSTEMI) referred for urgent coronary angiography and possible percutaneous intervention (PCI) with a drug-eluting stent (DES), according to possible earlier management in the Emergency Department (ED). UFH, unfractionated heparin.

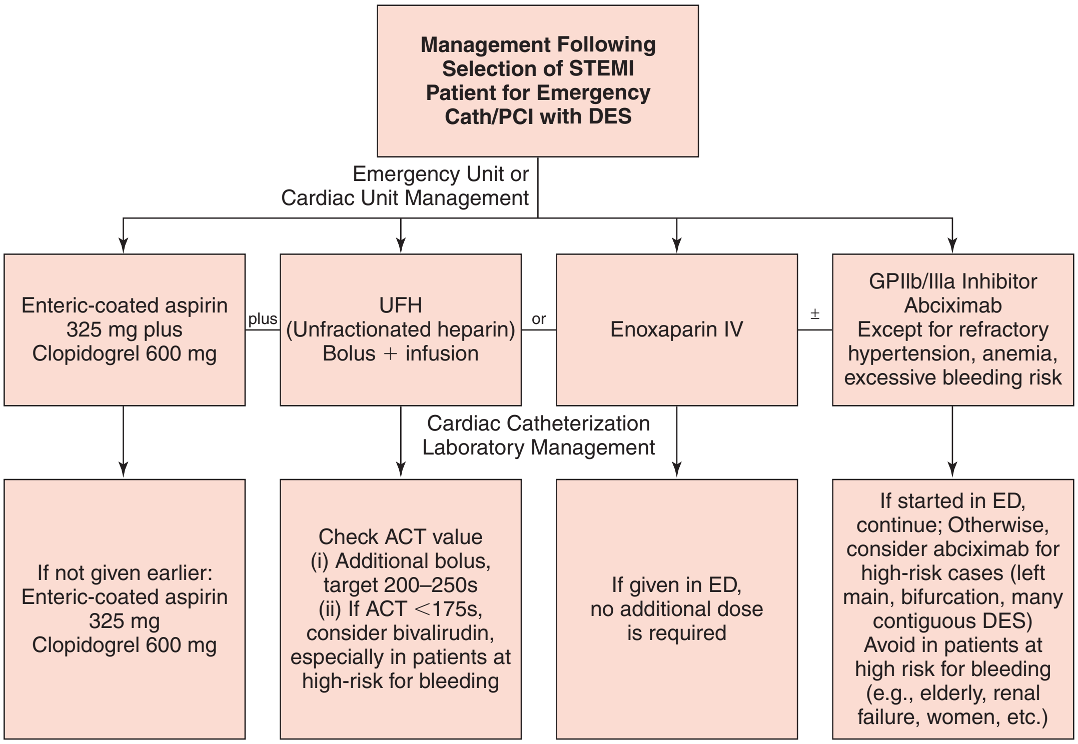

Figure 7–7 Algorithm for medical management of a patient with acute ST-elevation myocardial infarction (STEMI) referred for emergency coronary angiography and possible percutaneous intervention (PCI) with a drug-eluting stent (DES), according to possible earlier management in the Emergency Department (ED). UFH, unfractionated heparin.

specifically considered in patient subsets at high risk for bleeding complications.[106]

The indication for use of bivalirudin without a glycoprotein IIb/IIIa inhibitor for treatment of acute coronary syndromes stems from the ACUITY trial (Gregg W. Stone, MD, oral presentation at i2/ACC-2006 conference, March 7-11, 2006, Atlanta, GA). Use of this agent upon admission or transfer was associated with significantly less bleeding and similar ischemic protection compared with heparin plus a glycoprotein IIb/IIIa inhibitor. Of note, this is the first large acute coronary syndrome study wherein the PCI treatment included DES in a large proportion (>50%) of patients.

ACS patients treated with early glycoprotein IIb/IIIa inhibitor therapy should be maintained on these agents throughout the DES implantation procedure (see Figs. 7–6 and 7–7). Amendments of general guidelines regarding combination anticoagulation strategies are drawn from clinical trials that do not specifically demand DES use, but glycoprotein IIb/IIIa inhibitors should be specifically considered in all DES case subsets at high risk for stent thombosis (see earlier). Although no specific data have shown reduction of DES thrombosis with these agents, abciximab has decreased thrombosis after non-DES intervention in the highly thrombogenic state of acute myocardial infarction; interestingly, in this setting, bifurcation lesions were also found to predict early (within 1 month) thrombosis.[70] After completion of the DES implantation procedure, continuation of heparin, enoxaparin, or bivalirudin is no longer necessary and glycoprotein IIb/IIIa inhibitor infusion (when such agents have been used) should be continued for 12 to 18 hours.

A clinical trial reported specifically on the benefit of abciximab in patients with troponin (+) acute coronary syndrome who have been managed with aspirin, 600 mg of clopidogrel, and heparin until arrival at the catheterization laboratory.[107] The abciximab arm had 25% less adverse cardiac events. In such patients, abciximab has a more robust body of data than other glycoprotein IIb/IIIa inhibitors. DES were used in approximately one half of the enrolled population. No significant benefit of abciximab was documented in troponin (–) patients; hence, the use of glycoprotein IIb/IIIa inhibitors in such patients may not be necessary unless other high-risk features are present.

A recommendation for oral antibiotic prophylaxis before minor surgical procedures during the first 3 months after stent implantation has been customarily included in our practice. This is based on the low treatment risk and the potentially grave outcome of endovascular stent infection despite the absence of specific data that substantiate the necessity of such recommendation. It should be noted, however, that cardiac stent infection has not been noted even in the presence of sepsis.

Long-Term Antiplatelet Therapy

Because the time course of DES thrombosis can be more extended after implantation, although its incidence is similar or only marginally higher than after bare-metal stent, long-term oral antithrombotic therapy is particularly critical. Almost concurrently with the clinical approval of DES, data emerged favoring the prolonged duration of dual antiplatelet therapy (with aspirin plus clopidogrel) after bare-metal stent implantation either electively[108] or in the context of an ACS.[109] Given the initial thrombosis concerns with DES, these findings were quickly adopted in DES treatment recommendations that were included in essentially all DES clinical trials. Accordingly, the ACC/AHA PCI guidelines recommend treatment with aspirin 325 mg and clopidogrel 75 mg for 3 months for the sirolimus stent and 6 months for the paclitaxel stent.[104]

In clinical practice, our recommendation includes a reduction of the aspirin dose from 325 mg to 81 mg after the first month (in an attempt to limit minor bleeding) and extension of clopidogrel therapy for at least 1 year (and potentially even longer if no specific adverse reactions arise). The ACC/AHA PCI guidelines advise a 3- to 6-month course of 325 mg of aspirin in addition to clopidogrel; this recommendation stems from the original DES pivotal studies[5,17] and is not based on any evidence of superiority over the 81 mg dose of aspirin and has not altered our clinical practice as stated.

Long-term compliance should be highlighted to the patient, especially because stent thrombosis (despite its rarity) can be a truly major cardiac event. It is not unreasonable to state that if patient noncompliance has been a clearly documented issue in the medical history, DES therapy may need to be withheld. Bare-metal stent restenosis is a far less morbid condition than the rarer DES thrombosis; all health care providers should be engaged in this type of risk-benefit discussion on an individualized patient basis.

A specific case that warrants clarification is the treatment after DES placement in patients who are on long-term anticoagulation with warfarin. After bare-metal stent placement, lifelong aspirin dose of 81mg, plus warfarin with unmodified target international normalized ratio plus 1 month treatment with clopidogrel has been generally recommended to provide adequate anticoagulation for both conditions, with the understanding that the higher bleeding risk would be limited only to the first month. This risk can be considerably high if the triple therapy is to be prolonged to 6 to 12 months after a DES. For this reason, patients who require a very high international normalized ratio for unusual conditions or multiple valve replacement may not be the best candidates for treatment with multiple DES. Lower risk patients with atrial fibrillation may be treated with triple therapy, but tight control of the international normalized ratio 2.0 to 2.5 is recommended.

Medication Allergy

Specific issues can arise in cases of antiplatelet medication allergy (Fig. 7–8). Desensitization should be performed for elective cases.[104] For patients with an absolute aspirin contraindication, cilostazol 100 mg twice daily may be used in combination with clopidogrel. Ticlopidine 250 mg orally twice daily can be used for patients with an absolute clopidogrel contraindication, with the understanding of the need for periodic complete blood count checks and of the possible development of ticlopidine allergy.[110,111] In case of a contraindication to both ticlopidine and clopidogrel, then cilostazol may be used in combination with aspirin and with the understanding that the antiplatelet coverage may be suboptimal long term. If such a situation is known, preprocedure use of glycoprotein IIb/IIIa inhibitor and avoidance of DES should be considered, especially if complex patient, lesion, or clinical situations coexist. If medication allergy is suspected early post-DES implantation, the first actions should be (1) establishment of diphenydramine regimen; (2) steroid therapy; and (3) exclusion for other allergy causes (other new medication

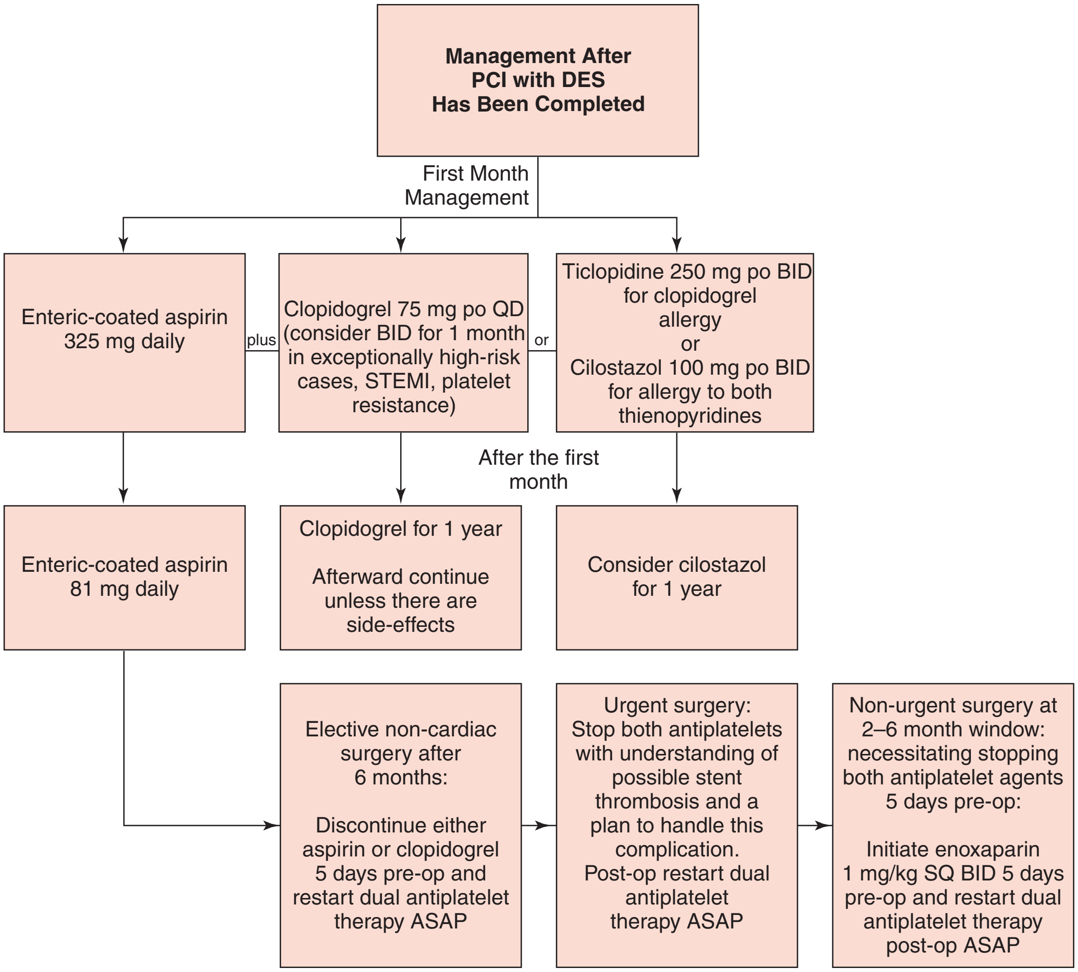

Figure 7–8 Algorithm for medical management of a patient who has been treated with a percutaneous coronary intervention (PCI) and received a drug-eluting stent (DES). ASAP, as soon as possible; BID, two times daily; SQ, subcutaneously.

or delayed contrast media reactions) rather than simple discontinuation of aspirin or clopidogrel. Clinicians should be extremely reluctant to change antiplatelet therapy within the first month after a DES and this reluctance should extend to 1 to 3 months if at all possible. Patients with an absolute need for changes in antiplatelet therapy in these time frames should be under frequent cardiologic follow-up. Finally, data on triple antiplatelet regimen are emerging.[112]

Antiplatelet Therapy Interruption

After DES implantation, the patient and family should be clearly informed that discontinuation of either antiplatelet drug should be undertaken *only* after a clear discussion of the matter with the interventional cardiologist who performed the DES procedure. This may occasionally be necessary owing to bleeding complications or surgery. The approach to each one of these situations should be individualized.

Severe (life-threatening) bleeding complications necessitate prompt interruption of all antithrombotic medications. Patients who have received DES are of particular concern because of the risk of stent thrombosis, especially if the antiplatelet agents are discontinued close to the time of DES implantation. The cause of bleeding should be evaluated and rectified as soon as possible (e.g., ulcer cauterization, packing of the nose for epistaxis) and antiplatelet therapy resumed as quickly as possible. Regular cardiology follow-up is necessary during the entire work-up of the bleeding complication. Because of the complicated nature of antiplatelet therapy interruption, preventive use of proton-pump inhibitors should be considered in patients at risk for gastrointestinal complications.

Performance of cardiac surgery under dual antiplatelet therapy is thought to have high bleeding complications. Although this has not been unequivocally documented, it is a matter of controversy in cardiothoracic surgical programs, and many surgeons recommend aspirin monotherapy for 3 to 5 days preoperatively with concomitant use of anticoagulation with heparin until the day of operation. Once a bypass procedure is performed, the issue of DES thrombosis may no longer be clinically relevant and postoperative antiplatelet therapy can be modified more liberally on an individualized patient basis. The status of antiplatelet therapy must be ascertained before patient discharge after careful review of the angiogram, DES implantation locations, and bypassed vessels.

Performance of non-cardiac surgery is much more complicated (see Fig. 7–8), because there is additional postoperative prothrombotic risk. In addition, the operative bleeding risk may vary significantly between procedures. Requests for complete interruption of all antiplatelet therapy 7 to 10 days

preoperatively should be routinely rejected in patients with DES, especially if complex patient, lesion, or clinical situations coexisted at the time of implantation. Direct communication between the surgeon and the cardiologist should explore possibilities to perform the surgical procedure (biopsy or operation) while antiplatelet monotherapy is continued, skipping one dose on the day of the procedure. The second antiplatelet drug could be interrupted 3 to 5 days preoperatively and resumed just after the operation. Procedures that would pose extended restrictions to oral intake postoperatively pose particularly high risk for DES thrombosis. The time of operation in relation to DES implantation is also very important. All elective surgery should be postponed for 6 months after DES placement. A relatively urgent operation with very limited need for pre- and postoperative antiplatelet therapy interruptions could be performed 2 to 3 months after DES placement in low-risk patient and lesion subsets. Emergency operations should be performed under close cardiology consultation. The remaining variety of intermediate urgency and risk cases should be performed with individualized arrangements agreed on by the surgeon and the cardiologist after taking into account the aforementioned recommendations.

FUTURE DIRECTIONS

Development of new DES systems is a topic of intense preclinical and clinical research. The limitations of the current DES systems frame the direction for future research. Improved efficacy in the high-risk patient, lesion, and clinical syndrome subsets is needed. The perception of marginally higher tendency for thrombosis with DES requires strict long-term compliance and poses questions regarding the adjunct pharmacotherapy as well as serial practical issues during subsequent treatment options—even for noncardiac diseases.

New DES research is investigating ways to make these devices even better through (1) improvements of the stent platform to facilitate the technical aspects of the procedure; (2) modifications of the polymer system to decrease potential adverse long-term local effects and improve controlled drug-delivery; and (3) experiments with newer generations of active substances or combinations with a second antithrombotic or vasculoprotective compound.

Regulatory approval of any modified device is not, however, as simple as previously granted approvals for advanced bare metal stent generations. A new DES system should be proved clinically to be non-inferior to an existing approved DES, and it should at the same time address at least one of the limitations of the current DES to have a meaningful role (see Chapter 4). The continuously elevated requirements for approval and clinical use undoubtedly pose hurdles to fast approval of new DES, but at the same time contribute to enhanced device safety and efficacy and have the potential to benefit increasingly more patient subsets and clinical conditions.

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Chapter 8

Revascularization Options for Ischemic Heart Disease: Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention

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CHAPTER CONTENTS

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are the most commonly performed major procedures in the world today. It is estimated that approximately 550,000 CABG and 1,000,000 PCI procedures are now performed each year in the United States, and that these interventions account for a significant proportion of health care expenditures. Estimated health care costs associated with treatment of coronary artery disease (CAD) and revascularization range from \$12 to \$20 billion each year.[1] As a consequence, CABG and PCI have undergone intense scrutiny by the public, medical profession, governmental organizations, and third-party payers. Large national databases have been gathered to monitor outcomes of individual physicians, hospitals, and regions and to ensure quality improvements where necessary. In 1989, the Society of Thoracic Surgeons (STS) established a national database for cardiac surgery.[2] This database now contains information regarding cardiac surgical procedures in more than 2.2 million patients who had surgery during a 10-year period (1995 to 2004), and of these, 73% underwent isolated CABG. Similar databases also exist for PCI. These include the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) with 6-year data on 800,000 patients, and the New York State Coronary Angioplasty Reporting System database.[3,4] Numerous publications and initiatives have been based on these surgical and angioplasty databases.

There are three broad indications for myocardial revascularization: to improve prognosis (probability of survival); to improve symptoms; and to prevent nonfatal events such as myocardial infarction (MI), arrhythmias, or heart failure. Indications for revascularization and comparisons of modes of revascularization have been well studied in large national databases and prospective randomized clinical trials and, for many patients, selection of treatment is often clear cut and well established. However, as pharmaceutical and interventional therapy evolves, the best form of revascularization continues to be debated for a significant number of patients.

EFFECTIVENESS OF REVASCULARIZATION: CABG

The early randomized trials of the 1970s first established CABG as an effective treatment for angina pectoris. These trials included the European Coronary Artery Surgery Study (ECSS),[5] the Veterans' Administration Cooperative Study (VA),[6] and the Coronary Artery Surgery Study (CASS).[7] The outcomes of these studies indicated that CABG was more effective than medical therapy in relieving angina pectoris and that bypass surgery improved the likelihood of long-term survival in patients with >50% left main stenosis and triple-vessel disease, particularly with decreased left ventricular function (ejection fraction [EF] <50%), and in patients with two-vessel disease and a left anterior descending (LAD) artery stenosis >50%. However, these early trials tended to include low-risk patients, and only 20% of these patients had an EF <50%. Almost all patients were males between 40 and 60 years of age, and medical therapy was limited to nitrates and β-blockers. At that time, aspirin and lipid-lowering agents were not in general use for patients with coronary artery disease.

The mean age of patients undergoing CABG is now 68 years,[2] and these patients are more likely to have diabetes mellitus, renal impairment, hypertension, cerebrovascular disease, chronic lung disease, impaired left ventricular function, extensive triple-vessel disease, and to have undergone an earlier procedure—usually percutaneous revascularization with or without stent deployment. Since these early trials, there have been significant advances in the medical, percutaneous, and surgical management of CAD. β-Blocker use is now more widespread, and the introduction of newer antiplatelet agents, HMG-CoA reductase inhibitors, and ACE inhibitors has revolutionized the medical management of these patients. Percutaneous revascularization techniques are now common and continue to evolve with advanced technology, improved operator skills, uncoated and coated stents, adjuvant therapy, and bradytherapy. The operative and perioperative management of patients who undergo bypass

surgery has also improved, with greater use of arterial grafting, less invasive procedures, and better attention to secondary prevention. Whereas at the time of the CASS study only 14% of patients received an internal mammary artery (IMA) graft,[7] almost all patients now undergoing CABG receive at least one arterial graft, usually the left IMA.

EFFECTIVENESS OF REVASCULARIZATION: PCI

PCI versus Medical Therapy

A meta-analysis of six prospective randomized clinical trials (RCTs) (see Chapter 1), compared balloon angioplasty and medical therapy and involved 1904 patients with nonacute coronary artery disease.[8,9] Among low-risk patients with symptomatic coronary artery disease (CCS class II or greater angina and average mortality <1% per year), balloon angioplasty clearly provided superior control of angina pectoris but was associated with a greater need for subsequent CABG. There was no significant impact on subsequent death, MI, or subsequent balloon angioplasty. These data suggested that balloon angioplasty was indicated if the desired level of anginal relief and physical activity could not be achieved with medical therapy alone and that prophylactic balloon angioplasty could not be recommended for the treatment of coronary artery disease in the absence of angina or ischemia.[9] However, most of these studies were undertaken before 1997 and reflected practice patterns that were prevalent at that time. Initial experience with balloon angioplasty was plagued by restenosis, with a need for repeat procedures of up to 34% of patients at 1 year.[10]

Bare-Metal Stents

The high incidence of restenosis after balloon angioplasty was initially addressed with the introduction of bare-metal stents (BMS). Initially introduced for the treatment of coronary dissections after balloon angioplasty, BMS were rapidly adopted by clinicians for routine use during balloon angioplasty, thus leading to immediate improvements in procedural safety and success. In particular, the rate of emergency CABG fell from about 5% to <1% and angiographic success became routine and independent of lesion morphology. The short-term therapeutic effects of these stents have been evaluated in several trials[11-13] and, although restenosis was significantly reduced, it continued to be a significant clinical problem following angioplasty (Fig. 8–1).[11] A meta-analysis of 25 randomized clinical trials involving BMS versus balloon angioplasty, by the National Institute of Clinical Excellence for the National Health Service of the United Kingdom, found that there were no significant differences in the overall mortality rates or the incidence of MI at 4 to 11 months of follow-up. More importantly, however, stent deployment lowered the probability of repeat revascularization procedures by nearly 50% (12.4% versus 20.6%).[13]

Drug-Eluting Stents

Despite the introduction of BMS, restenosis continued to be the chief limiting factor of percutaneous revascularization. Consequently, numerous agents have been used as stent

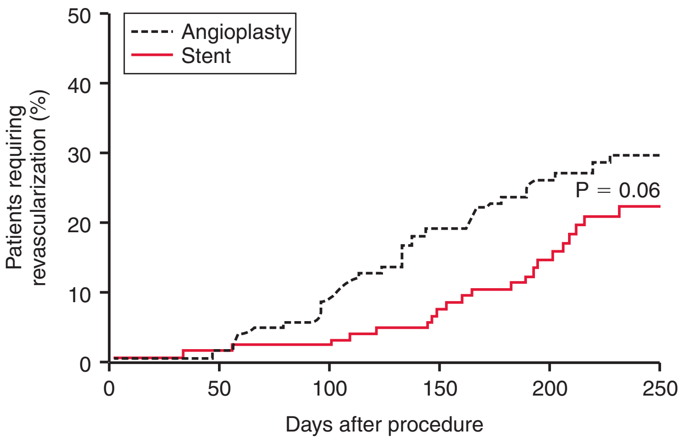


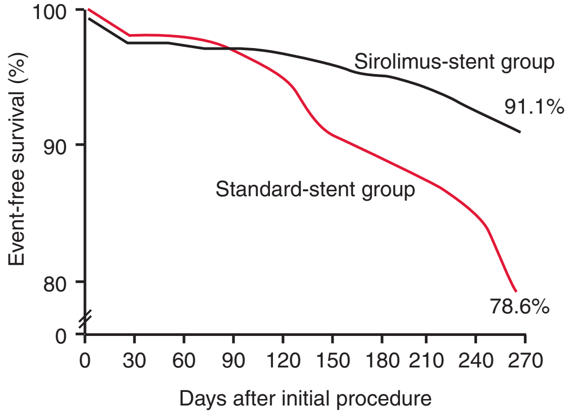
Figure 8–1 Kaplan-Meier curves for revascularization of the target lesion. Fewer patients in the stent group than in the angioplasty group required revascularization of the target lesion because of ischemia. (Adapted from Fischman DL, Leon MB, Baim DS, et al: A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496-501, with permission.)

coatings in the hope of preventing thrombosis, neointimal proliferation, and subsequent restenosis. These included antithrombotic (heparin), antiproliferative (paclitaxel, actinomycin-D), immunosuppressive (sirolimus) and anti-inflammatory (dexamethasone) agents. Nondrug polymers (e.g., phosphorylcholine, which inhibits platelet aggregation) have also been used. Two agents, sirolimus and paclitaxel, are now approved as antiproliferative drugs for drug-eluting stents (DES).[14] The polymer used to bind the drug in the DES controls the rate of release of the drug into the arterial wall. All currently approved DES are a device-polymer-drug combination.

Midterm results from several randomized clinical trials and a meta-analysis of DES versus BMS suggest that, compared with BMS, DES substantially lower rates of angiographic restenosis and the subsequent need for repeat revascularization (Fig. 8–2).[15-17] Although there is no evidence of reduction in the rates of death and MI, these studies have not been powered sufficiently to examine such particular outcomes. The reduction in major adverse cardiac events in the DES trials can be attributed entirely to reduction in repeat target lesion revascularizations.

It has also been recognized that certain stent designs and characteristics are associated with improved clinical outcomes. These include slotted tube stents versus coil stents,[18] second generation stents,[19,20] and stents with thinner struts.[21,22] Newer stent designs have been developed in the hope that they will further reduce restenosis rates. These include thin strut stents that use the non-bioabsorbable polymer phosphorylcholine to release the sirolimus analog ABT-578, stents with a highly deliverable cobalt-chromium metal alloy platform,[23] and biodegradable stents which provide the scaffolding to prevent abrupt vessel closure in the acute phase and then gradually disintegrate.[24]

Concern has been expressed that the relatively short clinical and angiographic follow-up in most DES trials of 6 to 12 months may be too short for delayed progression of neointimal hyperplasia to become apparent.[25,26] Thus far, long-term



No. at Risk

Sirolimus stent	533	529	527	524	520	515	509	505	493	477
Standard stent	525	523	521	514	506	481	474	465	451	436

Figure 8–2 Actuarial rate of survival free from target-vessel failure among patients who received either a sirolimus-eluting stent or a standard stent. The rate of event-free survival was significantly higher in the sirolimus-stent group than in the standard-stent group ($P < 0.001$ by the Wilcoxon and log-rank tests). (Adapted from Moses JW, Leon MB, Popma JJ, et al: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-23, with permission.)

follow-up data from observational studies of sirolimus-eluting stents do not suggest a late "catch-up" in neointimal hyperplasia.[27,28] Low rates of target lesion revascularization and of other major adverse cardiac events up to 3 years after device implantation were found in the RAVEL trial.[29] Rates of major adverse cardiac events at 3 years were 15.8% in patients randomly assigned to sirolimus-eluting stents versus 33.1% in patients assigned to BMS ($P = 0.002$).

As with most new technology, trials performed to assess safety and efficacy enroll only a small proportion of the entire universe of patients with CAD that would be potentially eligible for DES. Multi-lesion PCI with DES was not included in any trial. Patients with a recent MI or a low EF were also excluded. Lesion length and reference vessel diameter of the treated vessels usually reflect low-risk discrete lesions in medium-caliber vessels. On the basis of these variables, the patients enrolled in the DES trials have had a low risk of angiographic restenosis in general.[17] (See Chapters 6 and 7 for further discussion).

RELATIVE BENEFITS OF PCI AND CABG

Considerable controversy has existed and continues to exist regarding the relative benefits of PCI versus CABG. Up to 15 randomized trials comparing PCI, with or without stents, and CABG have been published and were reviewed extensively by both Eagle and colleagues[30] and Hoffman and associates.[31] In summary, these trials have shown that CABG tends to give better relief of angina with less need for repeat procedures than does PCI. However, initial costs are lower with PCI, complications occur less frequently, and patients are able to return to work earlier. Because of the greater need for reinterventions, PCI patients generate similar costs over the long term. Long-term survival tends to be similar with the two forms of treatment, except for diabetic patients for whom CABG is the superior treatment. In the meta-analysis reported by Hoffman,[31] for patients with multivessel disease, CABG provided a survival advantage at 5 to 8 years, and for diabetics, a survival advantage at 4 years (Fig. 8–3). Stents reduced the need for repeat procedures by about 50%.[31] Unfortunately, patients enrolled in such trials are not always representative of the global population of patients with CAD; therefore, the results of such trials are not necessarily applicable to the general population of patients. Indeed, only 5% of screened patients with multivessel disease were enrolled in these trials, and patients with left main coronary artery disease were excluded from such studies.

Registry studies have also provided valuable information regarding the relative benefits of medical therapy, PCI, and CABG, particularly for the global population of patients with CAD. Jones and coworkers[32] reviewed the Duke database of 9263 patients with CAD who underwent PCI (2924 patients), CABG (3890 patients), or medical therapy (2449 patients) only. Patients were followed for a mean of 5.3 years. The anatomical severity of the coronary artery stenoses best defined the survival benefit from CABG and PCI versus medical treatment. All patients with single-vessel disease, except those with ≥95% proximal LAD stenosis, benefited from PCI compared with CABG. All patients with three-vessel disease, and those with two-vessel disease with a ≥95% proximal LAD stenosis, were best treated by CABG (Fig. 8–4). Similar findings were found in a review of 60,000 patients in the New York State PCI and CABG Registry (Fig. 8–5).[33] Patients with three-vessel disease or those with severe proximal LAD stenosis (one- and two-vessel disease) achieved improved survival with CABG when compared with PCI.

When considering revascularization in any particular patient, many factors need to be taken into consideration. These include the patient's age, coronary anatomy, extent of stenoses, technical suitability for either PCI or CABG, comorbidities, left ventricular function, urgency of the procedure, and, to some degree, patient preference. Both PCI and CABG provide good relief of symptoms in most patients who are appropriately selected. These procedures need to be considered complementary, and many patients will undergo both of these techniques of revascularization during their lifetime.

SPECIAL SITUATIONS

Diabetes Mellitus

The prevalence of diabetes mellitus in the United States is increasing rapidly, mirroring the rapid rise in obesity. In 1999, 4.9% of the U.S. population was estimated to be suffering from diabetes mellitus and by 2002, this had increased to 6.3%.[34-36] Of individuals older than 60 years, 18.3% are estimated to be diabetic. These demographic changes are almost certainly related to the aging of the population, sedentary lifestyle, poor diet, and obesity. This alarming increasing incidence of diabetes has important consequences related to CAD and its management, as well as for society as a whole. For type I diabetics, the mortality rate from cardiovascular disease is four times that of the general population[37] and by age 55 years, one third of these patients will have died from CAD.[38]

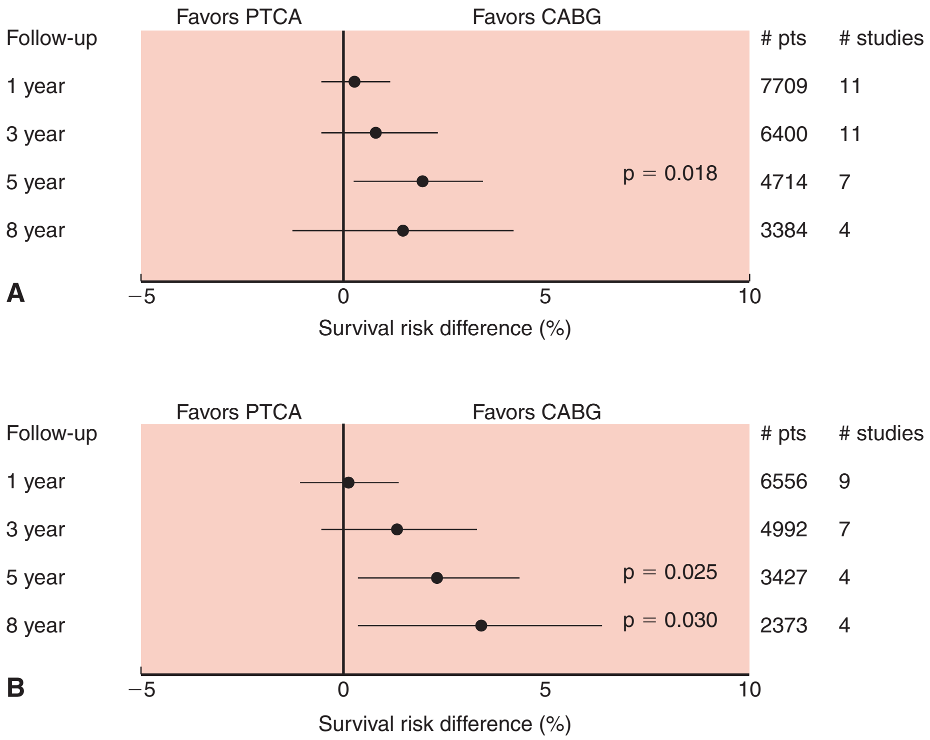


Figure 8–3 Risk difference for all-cause mortality for years 1, 3, 5, and 8 post-initial revascularization. All trials (**A**) and multivessel coronary artery disease (**B**). The *lines* represent 95% confidence intervals. Event rates for the coronary bypass arm at 1, 3, 5, and 8 years for all trials (**A**) were 3.0%, 4.7%, 7.1%, and 13.7%, respectively; for multivessel trials (**B**) event rates were 3.4%, 5.3%, 8.9%, and 15.8%, respectively. CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty. (Adapted from Hoffman SN, TenBrook JA, Wolf MP, et al: A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: One- to eight-year outcomes. J Am Coll Cardiol 2003;41:1293-1304, with permission.)

For type II diabetics, the incidence of atherosclerosis is estimated to be two to three times that of the general population.[39] The risk of an acute MI is 20% over 7 years, with a hospital mortality rate of 1.5 to 2.0 times higher than that for nondiabetics.[40] Moreover, diabetics who suffer an MI are more likely to develop congestive heart failure, cardiogenic shock, recurrent ischemia, and reinfarction, and poorer survival rate.[41] Thus, diabetes mellitus should be considered a cardiovascular disease as much as an endocrinologic problem, with both macro and micro-angiopathies.

The observed poorer clinical outcomes among diabetic patients with CAD are likely due to multiple factors—coexistent renal disease, hypertension, peripheral vascular disease, and the aggressive nature of the CAD itself. Compared with nondiabetics, diabetics are more likely to have left main disease,[42-46] multivessel disease, diffuse disease with smaller luminal diameters, and a larger number of lipid-rich plaques that are more prone to rupture.[47]

Indications for revascularization in diabetics are generally the same as those for nondiabetic patients. These include symptom improvement, left main disease, triple-vessel disease—particularly with decreased left ventricular function, and severe angina. However, diabetic patients are more likely to be asymptomatic than are nondiabetic patients, with significant myocardial ischemia. In the absence of angina, progression of ischemia with decreased left ventricular function may occur and this, in part, may explain the ultimate poorer prognosis in diabetic patients. In the absence of angina, the Asymptomatic Cardiac Ischemia Pilot (ACIP Study) showed that coronary revascularization was beneficial in selected patients.[48] In patients with known CAD, when therapy was directed by the onset of subsequent angina, the mortality rate at 2 years was 6.6%. Patients revascularized in the absence of angina but guided by the presence of ischemia had a mortality at 2 years of 1.1% (Fig. 8–6). Because of the asymptomatic nature of CAD in diabetics, an aggressive approach should be adopted in these patients to detect myocardial ischemia and to advise subsequent revascularization.

Data from the BARI trial suggest that for diabetic patients with two- and three-vessel disease, long-term survival is superior with CABG in comparison with PCI. In the BARI study,[49] the 5-year survival rate of treated diabetic patients was 73.1% (significantly less than the 91.3% for nondiabetic patients), emphasizing the serious impact that diabetes has on the outcome of patients with CAD, regardless of treatment. Diabetics in the BARI trial were also more likely to be obese, female, hypertensive, and have impaired renal function, peripheral vascular disease, and impaired left ventricular function. At 7 years, the mortality rate for CABG patients was 23.6% and for PCI patients 44.3%.[50] Similar data showing a trend toward improved results with CABG compared with PCI for diabetics were also observed in the Emory Angioplasty

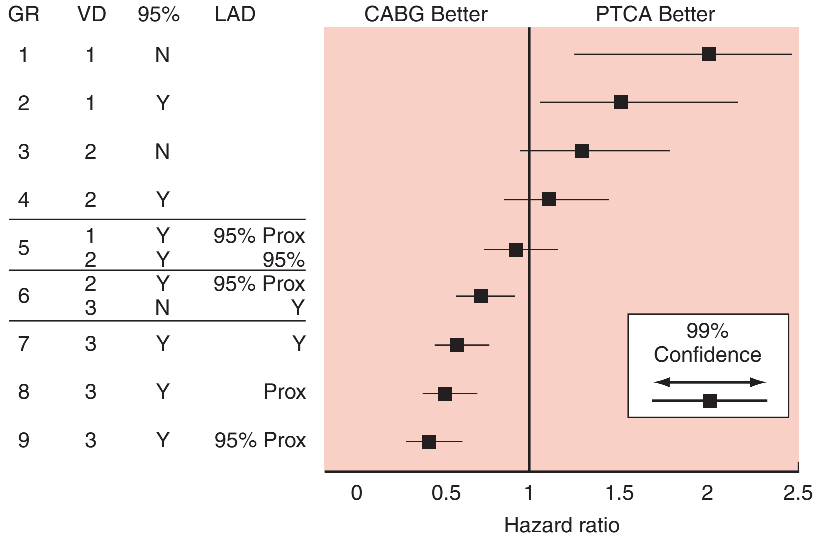


Figure 8–4 Adjusted hazard ratios comparing CABG and PTCA for the nine coronary anatomy groups. CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; Prox, proximal; VD, number of diseased vessels; 95%, ≥95% coronary artery stenosis. (Adapted from Jones RH, Kesler K, Phillips HR 3rd, et al: Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. J Thorac Cardiovasc Surg 1996;111:1013-25, with permission.)

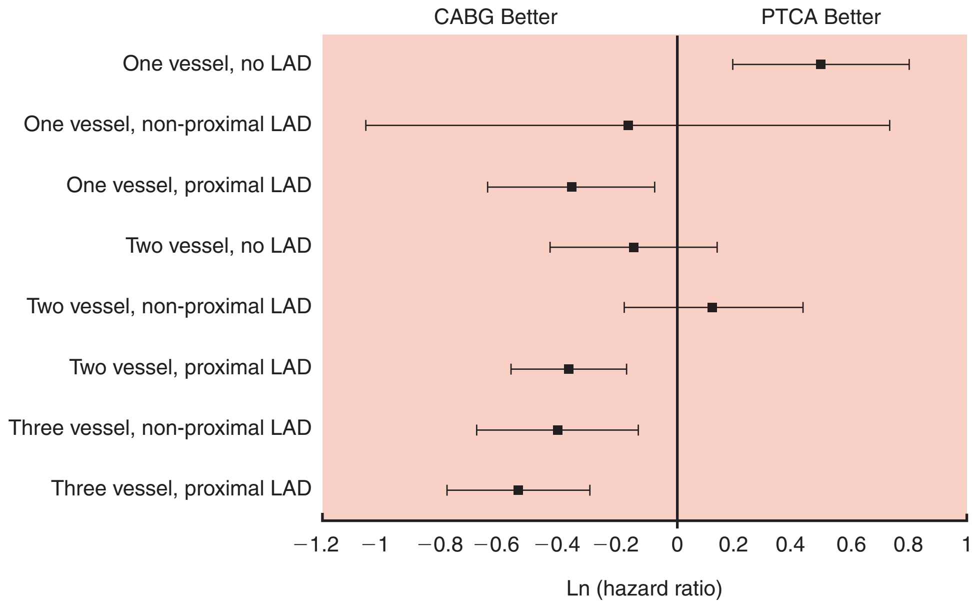


Figure 8–5 The 95% confidence interval for Ln (adjusted hazard ratio) of CABG patient death: PTCA patient death within a 3-year period (excluding patients with myocardial infarction less than 24 hours before procedure). CABG, coronary artery bypass graft; LAD, left anterior descending artery; PTCA, percutaneous transluminal coronary angioplasty;. (Adapted from Hannan EL, Racz MJ, McCallister BD, et al: A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1999;33:63-72, with permission.)

versus Surgery Trial (EAST)[51] (8-year mortality rate: CABG 24.5%, PCI 39.9%), and in the Arterial Revascularization Therapy Study (ARTS)[52] (3-year mortality rate: CABG 4.2%, PCI 7.1%). These observations were not reproduced in the BARI registry wherein the mode of revascularization was selected by physician preference.[53] In this registry, sicker and higher risk patients tended to be preferentially referred for CABG, whereas those with lesser degrees of CAD often underwent PCI. During follow-up, diabetic patients in the BARI Registry had equal survival rates when treated either by PCI or CABG.[53]

The improved survival rate seen in diabetics who undergo CABG appears to be contingent on the use of an IMA graft to the LAD coronary artery (7-year survival rate: 83.2% IMA, $n = 140$), whereas long-term survival of patients treated with saphenous vein grafts was similar to those treated with balloon angioplasty (7-year survival rate: 54.5% saphenous vein, $n = 33$).[54] Patients with an IMA graft showed a dramatic reduction in the mortality rate after a subsequent MI compared with patients who did not receive an IMA graft (Fig. 8–7).[54] Further data from BARI indicated that diabetics appeared to have more complete revascularization and less jeopardized myocardium at risk after CABG, compared with diabetic patients who were revascularized with PCI. Diabetic patients also had increased rates of restenosis after PCI compared with nondiabetics, whereas graft patency in those

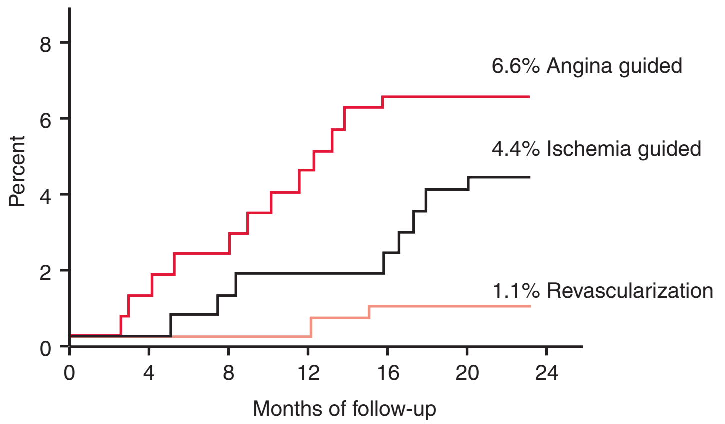


Figure 8–6 Two-year cumulative mortality rates for three treatment strategies. Significant differences were seen between revascularization and angina-guided strategies ($P < 0.005$) and between revascularization and ischemia-guided strategies ($P < 0.05$). Angina-guided and ischemia-guided strategies were not significantly different from each other ($P = 0.34$). The angina-guided strategy consisted of anti-ischemic drug treatment sufficient to control angina. The ischemia-guided strategy added additional active drug therapy if ischemia was still present during AECG recording. Patients in the angina-guided strategy received placebo to maintain blinding. The revascularization strategy consisted of initial treatment with PTCA or CABG aimed at achieving the most complete revascularization possible by the method deemed most appropriate by the physician. AECG, ambulatory electrocardiogram; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty. (Adapted from Davies RF, Goldberg AD, Forman S, et al: Asymptomatic Cardiac Ischemia Pilot [ACIP] study two-year follow-up: Outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037-43, with permission.)

undergoing CABG (venous and arterial) was not influenced by diabetic status.[55] These data suggest that the survival advantage of CABG in diabetics may be related to a more complete and more durable revascularization than that achieved by PCI. Current trials in the diabetic population with CAD are focusing on earlier revascularization and the use of insulin-sensitizing agents (BARI 2D)[56] and outcomes with DES in comparison with CABG (FREEDOM).[57]

Operative mortality and morbidity after CABG are increased in diabetics compared with nondiabetics, particularly insulin-dependent diabetics.[58] In a review of 41,663 diabetic patients registered in the STS Database, 30-day mortality rates in non-diabetic and insulin-dependent diabetics were 2.5% and 4.6%, respectively. Stroke, renal failure, and infective complications were also higher in insulin-dependent diabetics (Table 8–1).

Unstable Angina and Non-ST-Elevation Myocardial Infarction

Urgent coronary angiography with a view toward revascularization is now the preferred approach to the management of patients presenting with unstable angina and non-ST-elevation myocardial infarction (UA/NSTEMI). Although a number of theoretical advantages exist for an invasive approach, such as the establishment of a definitive diagnosis and triage to definitive therapy, the advantages of such an approach have only been recently verified with the reports of several contemporary trials.

Technological advances in PCI, including the use of stents and glycoprotein IIb/IIIa inhibitors, have facilitated this approach to the ACS. Data from the Mayo Clinic[59] confirmed the improving results of PCI for the management of unstable angina from the early days of coronary angioplasty to the late 1990s. In a population-based analysis of patients presenting with ACS in Olmsted County, Minnesota, between 1985 and 1992, the performance of early coronary angiography within 7 days of presentation was associated with a 37% risk reduction in mortality.[60] Three trials—FRISC-II, TACTICS-TIMI 18, and RITA-III—have also directly addressed the benefits of an early invasive strategy.[61-63]

Despite the clear demonstration of clinical superiority with the invasive approach, in the "real world" the proportion of patients with UA/NSTEMI who receive an early aggressive approach remains low. An analysis of 248 U.S. hospitals enrolled in the CRUSADE registry[64] showed that only 45% of nearly 18,000 patients with UA/NSTEMI had coronary angiography within 48 hours of presentation. Observed in-hospital mortality was significantly lower among patients with active early coronary angiography, in particular those at high risk as defined by a prospective risk score. In conclusion, the early invasive approach for management of UA/NSTEMI is preferred because it confers better clinical outcome—provided the resources exist to render rapid access to high-quality hospitals and experienced operators. The greatest benefit is seen in high-risk patients as characterized by those with positive biomarkers, electrocardiographic changes, and diabetes mellitus.

Primary PCI or CABG for STEMI

Perhaps the clinical subset in which percutaneous revascularization has had such a dramatic impact is in the treatment of ST-elevation myocardial infarction (STEMI).[65,66] Primary PCI (PPCI) is the preferred reperfusion therapy for STEMI. This statement, however, assumes that rapid diagnosis and triage to an experienced catheterization laboratory and team can be achieved. PPCI holds a number of theoretical advantages over lytic therapy for reperfusion, including the ability to visualize coronary artery anatomy and left ventricular function directly, and to provide direct mechanical reperfusion. Patients who

are best treated with medical therapy (e.g., mild disease or resolved thrombotic occlusion) or with surgical therapy (e.g., left main or extensive triple-vessel disease) can also be rapidly identified and triaged to the most appropriate therapy. Supportive measures and adjunctive imaging techniques, such as endotracheal intubation, intra-aortic balloon pumping and echocardiography, are immediately available in most therapeutic catheterization laboratories.

Although the widespread use of fibrinolysis and PPCI has largely superseded CABG for acute reperfusion of patients with STEMI, CABG still plays an integral role in the early reperfusion strategy for a small proportion of patients.[30,65,67] In the PAMI (Primary Angioplasty in Myocardial Infarction)-2 trial,[71] of 1100 patients with STEMI and without cardiogenic shock, 5% underwent CABG as the primary reperfusion strategy for STEMI. Mortality was 6.4% if surgery was undertaken on an urgent or emergency basis versus 2.0% if elective. Major risk factors for death included poor LV function and advanced age.

CABG early after STEMI may carry substantial risk, particularly in unstable patients with Q-wave infarction and decreased LV function. In these circumstances, the timing of such surgery may be important in determining ultimate outcome. Unfortunately, there are no clear guidelines as to when surgery should be undertaken.[65,68-71] In reviewing 11 retrospective and prospective observational studies regarding CABG and STEMI, Crossman and colleagues[71] concluded that timing of surgery after infarction was not necessarily an independent predictor of outcome. However, these studies did "appear to support an approach of medical stabilization for post-STEMI wherever possible to convert high-risk emergency operations to lower risk more elective procedures".[71] If stable patients with STEMI have preserved LV function and require surgical revascularization, then CABG can be undertaken within several days of infarction without an increased risk. In addition, for patients who have mechanical complications of STEMI (ventricular septal rupture or papillary muscle rupture), or who have ongoing ischemia that has been unresponsive to other medical therapy and have vessels suitable for bypass, surgery should be performed without undue delay.[65]

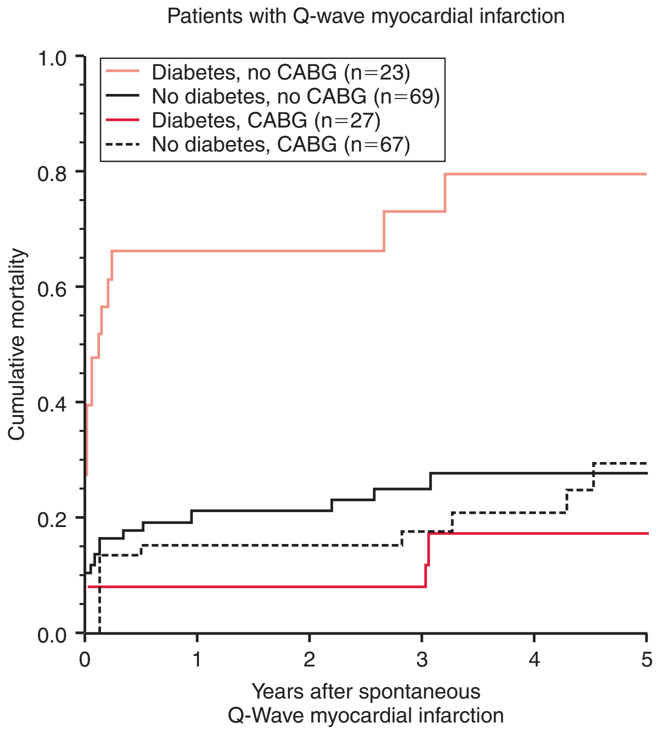


Figure 8–7 Mortality after the initial revascularization procedure. Kaplan-Meier estimates of the cumulative mortality in patients with spontaneous Q-wave myocardial infarction according to diabetes status and CABG status are shown (the numbers in parentheses refer to the 186 spontaneous Q-wave myocardial infarctions that occurred in 176 patients). Patients who did not undergo CABG were treated only with percutaneous transluminal coronary angioplasty. CABG, coronary artery bypass graft. (Adapted from Detre K, Lombardero MS, Brooks MM, et al: The effects of previous coronary-artery bypass surgery on the prognosis of patients with diabetes who have acute myocardial infarction. N Engl J Med 2000;342:989-97, with permission.)

Table 8–1 Mortality, Morbidity, and Infection in Diabetic and Nondiabetic Patients Undergoing CABG

	STS Database: CABG in 41,663 Diabetics			
	No Diabetes (%)	Diabetes (%)	Diabetes—Oral Medication (%)	Diabetes—Insulin (%)
30-Day Mortality	2.7	3.7	3.2	4.6
Morbidity				
MI	1.2	1.2	1.1	1.3
Stroke	1.4	2.3	2.1	2.4
Renal failure	2.9	5.4	4.3	7.1
Infection	5.2	7.9	6.9	9.4
Pneumonia	2.4	2.8	2.6	3.2
UTI	1.3	2.0	1.7	2.5
Sternum	0.5	1.0	0.8	1.4
Leg	1.1	2.3	1.9	2.7
Mortality and Morbidity	10.4	15.5	13.4	18.6

CABG, coronary artery bypass graft; MI, myocardial infarction; UTI, urinary tract infection. Modified from Carson JL, Scholz PM, Chen AY, et al: Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:418-23, with permission.

Patients who have had a significant decrease in LV function as a result of a STEMI and who are hemodynamically stable may benefit from a longer period of medical treatment to allow myocardial recovery to occur before surgical revascularization is undertaken. If a patient has critical coronary anatomy, such as >75% left main coronary artery stenosis, then CABG should be undertaken during the same hospitalization.[30,65]

Less-Invasive CABG

Before 1995, CABG had traditionally been performed with a sternotomy, full cardiopulmonary bypass, and cardioplegic arrest. However, a number of surgeons, particularly Benetti[72] from Argentina and Buffolo[73] from Brazil, gained extensive experience with CABG without cardiopulmonary bypass. This experience stimulated a renewed interest in minimally invasive CABG during the mid-1990s.

The MID-CAB (minimally invasive direct coronary artery bypass) is performed through a left anterior thoracotomy without cardiopulmonary bypass and is generally limited to bypass of the LAD coronary artery using the left IMA. Advantages of the MID-CAB included avoidance of cardiopulmonary bypass and its complications, reduction of operative and hospital costs, early discharge from the hospital, and a possible reduction in postoperative pain. Early anastomotic patency rates, however, were inferior to those treated with conventional CABG with cardiopulmonary bypass, and revascularization was usually limited to the LAD or diagonal coronary arteries. For these reasons, and because few patients with single vessel disease are currently referred for surgical revascularization, the MID-CAB failed to gain extensive use despite a wave of initial enthusiasm.

This initial interest in less invasive CABG led to further refinements in surgical techniques and instrumentation to allow bypass of multiple vessels in all three major coronary territories. Stabilization devices, coronary shunts, and better surgical approaches and techniques for cardiac positioning and improvements in anesthesia have promoted greater use of CABG without cardiopulmonary bypass or off-pump CABG (OP-CAB).[74-80] The advantages of OP-CAB surgery remain controversial, and there are wide variations in its use between surgical groups. It is well recognized that cardiopulmonary bypass may result in significant hematologic, metabolic, pulmonic, cardiac, renal, and neurologic complications, and it was hoped that OP-CAB would prevent these adverse sequelae. Most reports of OP-CAB surgery demonstrate a reduction in transfusion needs, shorter intensive care unit and hospital stays, and reduction in hospital costs.[83-84] There are no firm data indicating a definite reduction in neurological events in OP-CAB cases compared with CABG with cardiopulmonary bypass.

A number of randomized trials have also evaluated OP-CAB and CABG with cardiopulmonary bypass.[74,75,77,78] In a small randomized study of 281 patients by Van Dijk and coworkers,[77,78] the 30-day incidence of stroke was not significantly different in the conventional CABG group compared with the OP-CAB group (1.4% versus 0.7%). In reviewing the STS database, Cleveland and associates[79] reported on 11,717 (9.9%) OP-CAB patients and 106,423 (90.1%) cardiopulmonary bypass patients. The OP-CAB patients were older and had more dialysis-dependent renal failure and cerebrovascular disease than did the cardiopulmonary bypass patients. Emergency surgery and extensive triple-vessel CAD were more prevalent in the cardiopulmonary bypass group. The risk-adjusted mortality rate in the OP-CAB group was 2.31% and in the cardiopulmonary bypass group 2.93% ($P < 0.001$). The OP-CAB patients also had fewer strokes (1.25% versus 1.99%, $P < 0.001$), less renal failure, and less need for re-exploration for bleeding.

Initial experience with the OP-CAB procedures has been mainly related to low-risk patients with single- or double-vessel disease. Experience has shown, however, that patients most likely to benefit from this technique are those who would be at a high risk for complications of cardiopulmonary bypass.[79] These include elderly patients with cerebral, renal, or pulmonary disease or patients with significant calcification of the ascending aorta where cannulation or cross-clamping poses considerable neurologic risk. Small, diffusely diseased, or calcified coronary arteries or intramyocardial vessels make OP-CAB less attractive. The decision to perform an OP-CAB procedure will depend on a number of factors including age, associated comorbidities, size of the native coronary arteries, urgency of the procedure, and, above all, surgeon experience. OP-CAB surgery is more demanding than conventional CABG, and patients with unstable hemodynamics are better served by CABG that uses conventional cardiopulmonary bypass techniques. If the surgeon thinks that the patient will be harmed by an OP-CAB technique, then the operation should be abandoned and converted to a standard cardiopulmonary bypass procedure.

Concern exists regarding the long-term outcome of the OP-CAB procedure, particularly with regard to long-term patency of grafts, recurrence of angina, and the need for further interventions. Arom and associates[80] reported OP-CAB patients to have a higher risk of recurrent angina at 1 year when compared with patients having on-pump procedures. Sabik and coworkers.[81] also reported incomplete revascularization in OP-CAB patients. An American Heart Association (AHA) scientific statement, comparing on-pump with OP-CAB surgery, concluded that patients in general have excellent results with either type of procedure and that individual outcomes depended more on patient intrinsic factors rather than the type of procedure that was performed (Table 8–2).[82] At this time, CABG, using conventional cardiopulmonary bypass techniques, still remains the standard for surgical myocardial revascularization.

Endoscopic Vein Harvesting

A major advance in the minimally invasive approach to CABG is endoscopic saphenous vein harvesting. In the past, leg wound complications such as hematoma, cellulitis, and fat necrosis were common and represented a significant cause of morbidity in patients. This has been a particular problem in obese and diabetic patients. Endoscopic saphenous vein harvesting requires a 3-cm incision above the knee to identify the saphenous vein, followed by CO_2 insufflation of the tissues to follow the course of the vein, dissect and divide its branches, and finally remove the vein at the saphenofemoral junction (Fig. 8–8). Wound complications, time to ambulation, and hospital stays are significantly less with this technique and have produced improvement in patient satisfaction.[83,84] Histologic, electron microscopic, and endothelial cell analyses have demonstrated no differences between the two

Table 8–2 Findings Favoring OP-CAB or On-Pump CABG

Findings Favoring OP-CAB	Findings Favoring On-Pump CABG
Probably less bleeding	Less technically demanding
Probably less renal dysfunction	Shorter "learning curve"
Probably less short-term neurocognitive dysfunction, especially if aorta is calcified	Possibly better long-term graft patency
Possibly shorter overall length of hospital stay	Easier to graft posterior (circumflex) bypass targets
	Probably more bypass grafts constructed

CABG, coronary artery bypass graft; OP-CAB, on-pump coronary bypass. From Sellke FW, DiMaio JM, Caplan LR, et al: Comparing on-pump and off-pump coronary artery bypass grafting: Numerous studies but few conclusions: A scientific statement from the American Heart Association council on cardiovascular surgery and anesthesia in collaboration with the interdisciplinary working group on quality of care and outcomes research. Circulation 2005;111:2858-64, with permission.

Figure 8–8 Endoscopic vein harvesting from the left thigh.

techniques.[85] In this era, endoscopic vein harvesting should be considered the standard of care for most patients.

Minimally Invasive PCI

With improvements in technology, particularly stents and adjunctive pharmacologic therapy, success rates for elective and emergency PCI now approach 96% to 98%, and major procedural complications such as death, MI, or need for emergency CABG occur with frequencies of <1% each. Thus, the majority of procedural complications that occur now relate to the arterial access site. The femoral artery remains the preferred access site for the majority of interventional cardiologists and is susceptible to hemorrhage, hematoma, pseudoaneurysm, arteriovenous fistula formation, and retroperitoneal hemorrhage. The incidence of these complications is directly related to the severity of the underlying vascular disease, particularly in elderly and diabetic patients, as well as to sheath size and anticoagulant use. The availability of miniaturized equipment capable of being delivered through 6-Fr and even 5-Fr sheaths has mitigated the problem. Similarly, the realization that prolonged postprocedural heparin infusions are not necessary has contributed to a dramatic decline in the incidence of vascular complications after PCI. Such complications, however, still occur in 5% to 8% of patients after PCI.

A proposed solution to the problem has been to use the radial artery in preference to the femoral artery as an access site for invasive coronary procedures. Developed and popularized by the efforts of Campeau[86] and Keimineij,[87] transradial coronary angiography has gained popularity in Europe and selected U.S. and Canadian sites. The radial artery can accommodate 5-Fr to 7-Fr sheaths, allowing passage of standard caliber (majority 6 Fr) catheters to the heart for performance of diagnostic and therapeutic procedures. All procedures that can be performed from the femoral artery through 6-Fr guiding catheters may be performed from the radial artery through similar catheters. Because the artery is superficial, has no major adjoining neurovascular structures, and is easily compressible for achievement of hemostasis, the incidence of vascular complications is <1% in experienced hands. Bed rest is not necessary following transradial coronary angiography and this leads to superior patient comfort and satisfaction, and allows for the possibility of true outpatient PCI. Because of its small size, however, cannulation is not always successful and a proportion (generally <5% in experienced hands) of procedures will need to be converted to the femoral approach.

Robotic Surgery

Efforts have been undertaken to perform CABG by total endoscopic techniques.[88-90] Robotic-assisted surgery is performed by a surgeon sitting at a console and viewing the interior of the chest and surface of the heart with 3-dimensional vision. This is accomplished by using cameras that are precisely controlled using foot pedals. The computer-enhanced system filters out physiological tremor that arises from the surgeon's hands and allows precise movement of the robotic instruments. The endoscopic arms are equipped with microsurgical instruments with unlimited range of motion. It is hoped that these closed-chest video-assisted procedures will result in reduced surgical trauma, less pain, decreased bleeding and risk of infection, shorter hospital stays, and more expeditious resumption of normal activities compared with conventional CABG. Initial experience has been limited almost entirely to grafting the LAD and/or the diagonal coronary artery.[90] Many obstacles remain regarding implementation of total endoscopic robotic surgery. These include development of adequate stabilizers and sutureless anastomotic devices, and the extreme cost associated with robotic technology. Total endoscopic CABG is an extremely demanding procedure, and its technical difficulties and cost will need to be addressed before it becomes a standard procedure for both patients and surgeons.

In PCI, remote control of the catheters and wires has now become possible using the Stereotaxis magnetic guidance system. This technology uses two large (approximately 4000 lbs. each) permanent magnets on either side of the patient's body to establish a magnetic field surrounding the heart. The north-south dipole of the field can be manipulated using computer software, and, in combination with 3-dimensional reconstruction of coronary or cardiac anatomy, the operator can precisely steer magnetically enabled wires and catheters. Potential applications of the technology include facilitating PCI in tortuous or occluded vessels, placing biventricular pacing leads, or facilitating ablative electrophysiological procedures.[91]

Total Arterial Grafting

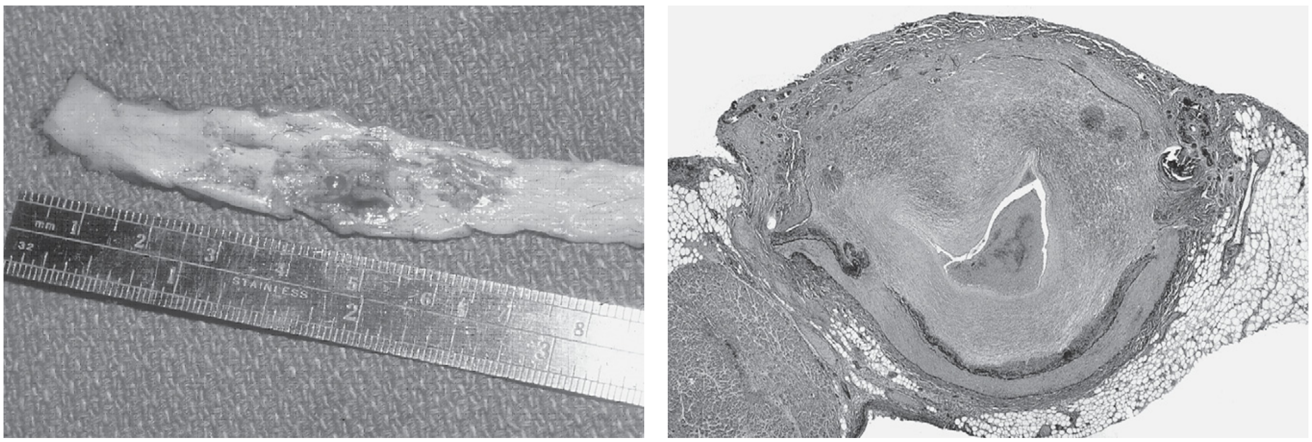
By the early 1980s it was apparent that the long-term patency of the saphenous vein was inferior to that of the IMA (sometimes referred to as the internal thoracic artery [ITA]). Saphenous vein grafts in the first 1 to 2 years may develop intimal hyperplasia and are later subject to vein atherosclerosis (Fig. 8–9). The patency of vein grafts at 5 years is 70% to 80% and at 10 years 40% to 50%. This compares with a 10-year patency rate for IMA grafts of >90%. In 1986, Loop and colleagues[92] demonstrated improved survival at 10 years in patients receiving IMA grafts compared with those receiving saphenous vein (93.4% versus 88%, $P = 0.05$ with two-vessel disease and 82.6% versus 71.0% $P < 0.001$ with three-vessel disease). Patients who received IMA grafts also had fewer subsequent cardiac events and less need for reoperations. The relative scarcity of smooth muscle cells in the thin-walled media of the IMA, combined with a well-formed internal elastic lamina even at advanced age, may be an important reason for its low susceptibility to atherosclerosis and a major determinant to its superior long-term patency as a coronary artery bypass graft.[93]

For patients requiring a graft to the LAD, the use of the IMA is the standard of care in almost all patients, including the elderly. In an analysis of more than 500,000 patients who underwent elective CABG in the United States between 1996 and 1999, the IMA graft was used in 94% of patients younger than 55 years of age and 77% of patients greater than 75 years of age.[2]

Surgeons may be reluctant to use the IMA in certain patients, particularly after STEMI, because of limited flow through the artery or graft and the time necessary to harvest it. In the PAMI-2 trial,[67] of 120 patients undergoing surgery, only 31% received an IMA graft; no patients had cardiogenic shock at the time of surgery. Data suggest that IMA grafts can be used safely soon after STEMI with no increase in mortality.[30,65] Moreover, their use is associated with better long-term survival. Hirose and associates[94] used arterial grafts in 96% of 47 patients undergoing emergency CABG within a mean of 27 hours from infarction, and the operative mortality rate was 6.4%. In a further study, Hirotani and coworkers[95] performed CABG on 98 patients within 30 days of infarction with a mortality rate of 7.4%. CABG without arterial grafts was the sole predictor of an adverse survival.

Because of the clear advantage of single IMA grafting, surgeons have promoted the use of other arterial grafts (right internal mammary, gastroepiploic) together with the concept of total arterial revascularization. Several authors[96-100] have shown increased survival in patients undergoing bilateral IMA grafts. Lytle and associates[100] published long-term results of bilateral versus single IMA grafts involving 1152 propensity matched pairs of patients with a mean follow-up of 16.5 years. Patient survival rates for the bilateral IMA and single IMA groups at 7, 10, 15, and 20 years were 89% versus 87%, 81% versus 78%, 67% versus 58%, and 50% versus 37%, respectively ($P < 0.0001$). As can be seen in Figure 8–10, divergence of the hazard function curves continued to widen, with an increased risk of death with single IMA grafting compared with bilateral IMA grafting through the 20 postoperative years of follow-up. Buxton and colleagues.[96] demonstrated a 10-year patient survival rate for bilateral IMA grafts of 86% compared with 71% for single IMA grafts. For patients younger than 60 years with a normal EF and no significant comorbidity, however, there was no difference in the survival rate. Most benefit was seen in patients older than 60 years with an EF < 35% and with diabetes mellitus (Fig. 8–11).

Concern exists regarding the increased incidence of sternal infection with the use of both IMA grafts (Matsa[97]—2.6%; Tector[98]—3%, Lev-Ran[101]—4%). Because the IMA is an important source of blood supply to the sternum, the use of



A B

Figure 8–9 **A,** Extensive atherosclerosis involving a saphenous vein bypass graft. **B,** Photomicrograph of a coronary artery-saphenous vein graft with fibrointimal atherosclerosis. The arterial segment (*lower portion*) shows both internal and external elastic lamellae. (Verhoeff van Gieson, 40×.)

both IMAs for grafting may have a serious effect on sternal blood supply and its subsequent healing. Attempts to minimize these effects have used techniques to skeletonize the IMA during harvesting, thereby minimizing the adverse effect of conventional IMA harvesting wherein the taking of a wide pedicle decreases sternal blood supply.[97] In this technique, the IMA is dissected free from all surrounding tissues, including the accompanying veins, fascia, lymphatics and adipose tissue, thus preserving the microvasculature in the surrounding tissues of the chest wall and sternum.

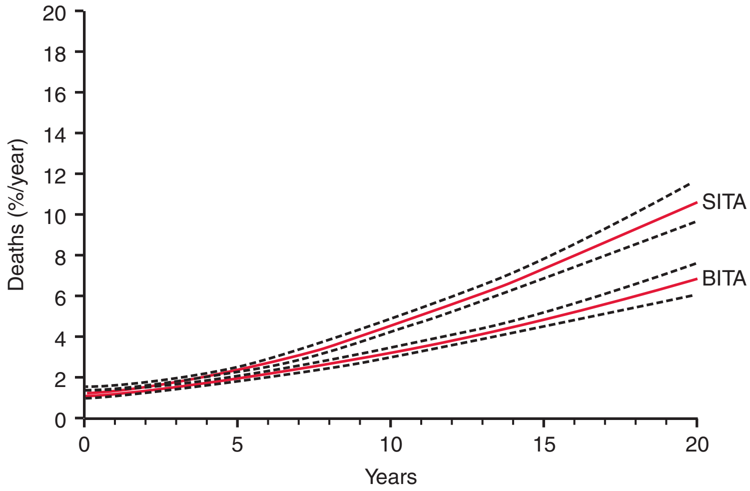


Figure 8–10 Hazard function curves demonstrate the increased risk of death associated with single internal thoracic artery (SITA) grafting with increasing follow-up interval. *Dashed lines* are 68% confidence bands. BITA, bilateral internal thoracic artery. (Note: The abbreviation ITA referring to the internal thoracic artery is synonymous with IMA, which stands for internal mammary artery.) (Adapted from Lytle BW, Blackstone EH, Sabik JF, et al: The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. Ann Thorac Surg 2004;78:2005-2012, with permission.)

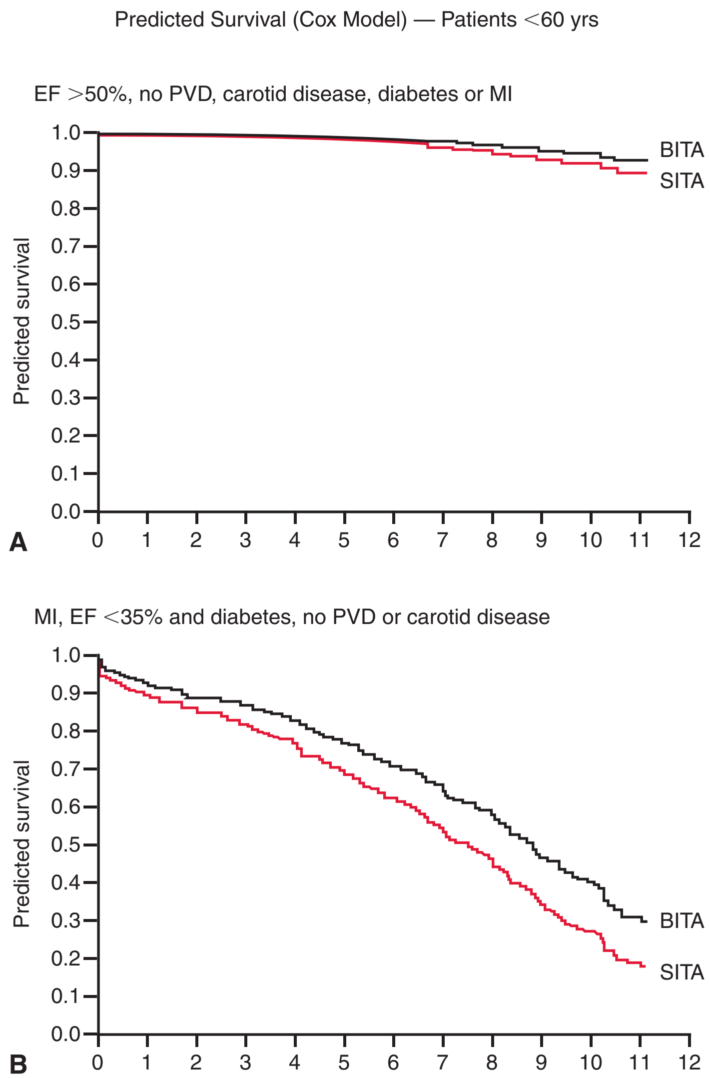
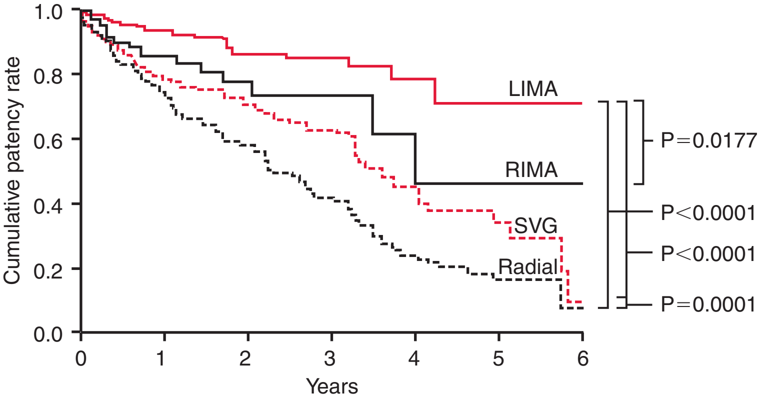


Figure 8–11 Predicted survival after coronary artery bypass surgery with bilateral ITA grafting or single ITA grafting in patients younger than 60 years adjusted for: **A,** Normal left ventricular function, ejection fraction (EF) > 50% without myocardial infarction (MI), diabetes, peripheral vascular disease (PVD), or carotid disease; **B,** previous MI, EF < 35% and diabetes, and absence of PVD and carotid disease. BITA, bilateral internal thoracic artery; SITA, single internal thoracic artery. (Adapted from Buxton BF, Komeda M, Fuller JA, Gordon I: Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery: Risk-adjusted survival. Circulation 1998;98[S19]:S10, with permission.)



No. at Risk

LIMA	265	146	89	38	17	3	0
RIMA	75	37	22	10	4	0	0
SVG	267	157	114	63	27	7	0
Radial	392	220	136	64	24	8	0

Figure 8–12 Kaplan-Meier curves of cumulative patency rates according to type of bypass graft. Radial artery grafts were associated with worst patency rate of all graft types. Four left internal mammary arteries (LIMA), two right internal mammary arteries (RIMA), five saphenous vein grafts (SVG), and six radial grafts were not included in this curve. (Adapted from Khot UN, Friedman DT, Pettersson G, et al: Radial artery bypass grafts have an increased occurrence of angiographically severe stenosis and occlusion compared with left internal mammary arteries and saphenous vein grafts. Curculation 2004;109:2086-91, with permission.)

There has also been renewed interest in using the radial artery as a conduit for CABG. Although the initial long-term patency of this vessel was poor when used by Carpentier in 1973,[102] better techniques of harvesting the radial artery, as well as the use of long-acting nitrates and/or calcium channel blockers to prevent spasm postoperatively, have improved outcomes. For patients in whom bilateral IMA harvesting may lead to a significant risk of sternal infection, use of a radial artery is a good alternative to a second IMA and can be used in most patients. Contraindications to its use include a positive Allen test, Dupuytren disease, and vascular disease of the upper limb. Ruengsakulrach and coworkers[103] found that the radial artery, when compared with the IMA, had a significantly greater incidence of intimal hyperplasia (94% versus 69%,) atherosclerosis (5.0% versus 0.7%), and medial calcification (13.3% versus 0%). They urged caution in its use in the elderly, diabetics, smokers, and patients with peripheral vascular disease.

Several studies have suggested better patency of the radial artery compared with the patency of the saphenous vein but not as good as that for the IMA. At 1 year, Tatoulis and associates[104] reported a radial artery patency rate of 91%. In a multicenter study, Desai and coworkers[105] randomized 561 patients to receive either a radial artery graft or a saphenous vein graft to a second coronary territory. Radial artery grafts were associated with a lower rate of graft occlusion at 1 year than were saphenous vein grafts. Because the patency of radial artery grafts depended on the severity of native vessel stenosis, such grafts should preferentially be used for target vessels with high-grade lesions.[109] Subsequently Khot and coworkers[106] from the Cleveland Clinic reviewed patency of grafts in patients who were restudied after CABG because of angina (60%) or an abnormal stress test (32%). Radial artery grafts had a patency of 51%, which was inferior to that of the IMA (90%) and saphenous vein (64%) (Fig. 8–12). Patency for women was worse than that for men (39% versus 56%). Further studies are warranted to determine the long-term fate of radial artery grafts before their routine use can be recommended, particularly for women.

Other techniques used to extend arterial grafting include sequential IMA grafting and composite grafting using one IMA or radial artery as a free graft anastomosed to the site of a second IMA pedicled graft (Fig. 8–13).[107] Factors to consider before deciding to use bilateral IMA grafts or other arterial conduits include patient age, diabetic status, urgency of the case, and presence of significant obesity. For example, a 75-year-old morbidly obese diabetic female should not undergo bilateral IMA grafting because of the subsequent risk of serious life-threatening sternal wound infection.

Coronary Revascularization (PTCA or CABG) and Noncardiac Surgery

Coronary revascularization is frequently performed to mitigate the potential risks of major noncardiac surgery. For example, diabetic patients with combined coronary and peripheral vascular disease represent an especially high-risk segment in whom the risks of postoperative MI, arrhythmias, and death are significantly higher than in the general population, especially if functional tests show prior MI or provocable ischemia. The universal availability of noninvasive testing and the attention to preoperative risk assessment has resulted in a substantial number of patients being referred for coronary angiography before major noncardiac surgery. Such patients frequently undergo PTCA, PCI, or CABG before elective noncardiac surgery. A report from Kaluza and coworkers[108] drew attention to an observed catastrophic outcome of noncardiac surgery that is performed too soon after coronary artery stenting. They reported on 40 patients who underwent noncardiac surgery within 6 weeks of coronary stenting with BMS. Of this group, 7 MIs, 11 major hemorrhages, and 8 deaths were reported, with the greatest risk observed within 14 days of the coronary procedure. A subsequent report[109] highlighted the risk of DES thrombosis occurring when all antiplatelet therapy, both clopidogrel and aspirin, was withdrawn to allow noncardiac surgery or endoscopic procedures, such as bladder or colon polyp removal, to be undertaken. Subacute thrombosis in this situation can be associated with a mortality rate approaching 50% and a nonfatal MI rate approaching 40%. Factors likely to contribute to postoperative stent thrombosis include withdrawal of antiplatelet therapy, incomplete endothelialization of stents coated with antiproliferative agents, and the prothrombotic metabolic milieu which occurs after major noncardiac surgery.

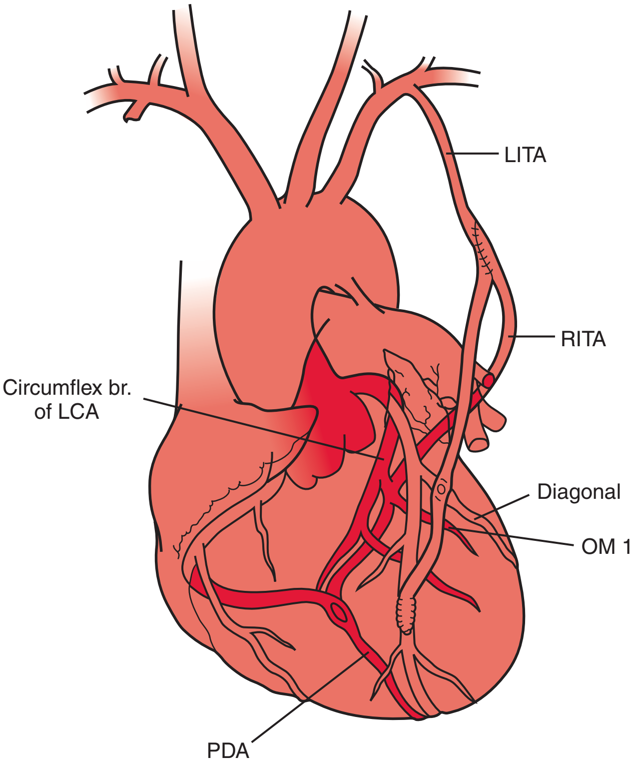


Figure 8–13 Total arterial revascularization using a pedicled left internal thoracic artery (LITA) graft to the left anterior descending (LAD) artery and diagonal and a free right internal thoracic artery graft (RITA) anastomosed proximally to the LITA and distally to the first obtuse marginal (OM 1) and to the posterior descending artery (PDA). Note: the LITA is sometimes referred to as the LIMA.

The development of ACS following the withdrawal of aspirin in patients with CAD has been reported[110] and essentially manifests as an acute STEMI. Both BMS and DES are susceptible to such a complication, although DES may be more vulnerable. Postoperative stent thrombosis can be extremely difficult to treat, with the attendant risks of inducing operative-field bleeding. One suggested approach is to categorize patients according to the competing risks of bleeding following noncardiac surgery and thrombosis of a coronary artery stent. Continuation of antiplatelet drugs should be considered if at all possible, and less invasive alternatives to noncardiac surgery, such as endovascular approaches to treatment of peripheral vascular disease, should be considered.

Earlier CABG, Hybrid Procedures, and Supported PCI

Despite an initial wave of enthusiasm, hybrid CABG and PCI procedures have not become commonly accepted.[111] Used primarily to refer to an off-pump, minimally invasive LIMA to LAD anastomosis (i.e., MID-CAB) in combination with stenting of other vessels either on the same day or at another time, the so-called hybrid procedure suffers major logistical problems. Patients need to undergo two separate procedures, often being subjected to hospitalization and separate sets of risks twice. Moreover, the subsequent less-than-ideal results of the MID-CAB approach to the LIMA to LAD anastomosis have dampened enthusiasm for this procedure, and it is not performed routinely.

Improved procedural outcomes and secondary prevention measures have led to a growing population of elderly patients with prior CABG, previous MI, severe left ventricular dysfunction and angina pectoris secondary to graft occlusion or disease progression. As patients continue to live longer after surgery, patients with patent left IMA grafts and occluded vein grafts are commonly encountered in clinical practice. In such patients, the risks of repeat CABG surgery are significantly greater than the risks of either primary CABG or PCI. Percutaneous interventional techniques on saphenous vein grafts are also associated with a higher incidence of periprocedural MI and death. Distal protection devices, either balloon occluders or filters, have been developed and can lower the risks of distal embolization in such circumstances. However, no good therapy to halt or retard the progression of vein graft disease exists. Statin and aspirin therapies are helpful but often not in the advanced stages of vein graft disease.

Comorbidities such as diabetes mellitus, peripheral and cerebral vascular disease, chronic renal disease, and hypertension are also common. Such patients frequently will have prohibitively high risks with standard repeat CABG or PCI. We have advocated a hybrid approach to such patients, whereby hemodynamic support is employed with either a surgically or percutaneously placed circulatory assist device, of which a number are available. The procedure is generally performed with the assistance of an experienced cardiac anesthesiologist who administers a general anesthetic with endotracheal intubation and central hemodynamic monitoring. The cardiac surgeon or interventionalist experienced in such techniques supervises the hemodynamic support with the circulatory assist device. In such a controlled situation, percutaneous techniques using rotational atherectomy and PCI can be performed with a measure of safety and assurance not achievable with either standard CABG or PCI.

Pre- and Postprocedural Care

Advances in periprocedural care have resulted in improved short- and long-term outcomes for patients who undergo CABG. Preoperatively, most of these improvements relate to optimization of blood glucose control and treatment of hyperlipidemia on admission to the hospital or on diagnosis of CAD. Several authors[112,113] have demonstrated improved outcomes for patients undergoing CABG who have been treated with HMG-CoA reductase inhibitors preoperatively. Pan and associates,[112] in reviewing a propensity-matched cohort of 1362 patients undergoing CABG, found that preoperative HMG-CoA reductase inhibitor use was independently associated with a significant reduction in the composite endpoint of 30-day mortality and stroke (7.1% versus 4.6%). Likewise, in a prospective randomized study, Christenson[113] demonstrated that 4 weeks of treatment with simvastatin (20 mg daily) prior to CABG resulted in a lower incidence of graft stenoses and subsequent interventions at 2 years compared with a group of patients who did not receive simvastatin.

For patients undergoing PCI, effective antiplatelet and antithrombin therapies are necessary during the pre-, intra-, and postprocedural care. Dual oral antiplatelet therapy with aspirin and clopidogrel is now the standard of care. In the preprocedural setting, patients presenting with ACS are treated

Table 8–3 Insulin Infusion Rates According to Blood Glucose Levels

Blood or Plasma Glucose (mg/dL)	IV Infusion Rate (mL/hr)	Insulin Infusion Rate (units/hr)
>400	16	8
350-400	12	6
301-350	8	4
250-300	6	3
200-249	5	2.5
150-199	4	2
120-149	3	1.5
100-119	2	1
70-99	0	0
<70	0	0

The standard algorithm is designed for an average 70-kg patient and may require modification for patients who are substantially larger or smaller. The standard IV insulin solution is 250 units of human regular insulin in 500 mL of 0.45% sodium chloride. Glucose goals should be defined for each patient. In the acutely ill patient or during the immediate perioperative period, a glucose range from 100 to 200 mg/dL is a reasonable goal. Reflectance meter glucose should be measured hourly until the glucose levels have stabilized in the goal range (100 to 200 mg/dL) for 4 hours. Frequency of testing may then be decreased to every 2 hours, and if the glucose control remains stable, to every 4 hours. The algorithm may be progressively increased by 50% increments for each glucose range ≥200 mg/dL if glucose does not decrease into goal range. Hypoglycemic risk is increased if the algorithm is increased for glucose <200 mg/dL.

with an antithrombin and a parenteral glycoprotein IIb/IIIa inhibitor (indicated for high-risk patients with diabetes mellitus, positive biomarkers, or electrocardiographic changes). During the procedure, oral antiplatelet therapy is continued and is frequently supplemented by a glycoprotein IIb/IIIa inhibitor to achieve 80% suppression of platelet activity. Antithrombin therapy is necessary but may be discontinued on completion of the procedure. Following the procedure, dual antiplatelet therapy is continued for a minimum of 1 month (elective BMS) to at least 1 year (DES for ACS). Attention to secondary preventive measures is mandatory for all patients undergoing PCI to minimize the risk of disease progression and the development of nonfatal MI or sudden death.

More widespread use of antiplatelet agents (aspirin) before surgical revascularization has also resulted in an improved patient outcome. In a study from the Mayo Clinic, Bybee and colleagues[114] showed that patients treated with aspirin within 7 days before CABG had a decreased incidence of subsequent death as well as cerebrovascular complications. There was no increased risk of returning to the operating room for bleeding, although transfusion requirements were higher in patients treated with aspirin. We believe that aspirin (81 mg to 325 mg) should be either commenced or continued in patients before surgery, particularly in those with ACS or unstable angina. Preoperative administration of clopidogrel is associated with a significant increase in postoperative hemorrhage and should be stopped, if practical, 5 to 7 days before CABG.[30,65,115] In a prospective study of 224 patients having CABG, Hongo and associates[116] found reoperation for bleeding to be 10-fold higher in patients who had received clopidogrel within 7 days of surgery than in those who had not received clopidogrel.

Several reports have emphasized the importance of maintaining normoglycemia in the surgical patient. Gandhi and coworkers[117] from the Mayo Clinic demonstrated that elevated intraoperative glucose levels during cardiopulmonary bypass were significantly associated with an increased mortality, and more frequent pulmonary and renal complications. Studies also suggest that improved outcomes in patients undergoing CABG can be achieved with better glucose control and the use of glucose, insulin, and potassium infusions during surgery. Lazar and colleagues[118] showed that patients who received a glucose/insulin/potassium infusion perioperatively had a significantly lower incidence of atrial fibrillation, a shorter postoperative stay, a survival advantage, and decreased episodes of myocardial ischemia and wound infection over the subsequent 2 years. Similar findings related to infection were also recorded by Furnary and associates.[119] Management of perioperative hyperglycemia should be undertaken with an appropriate algorithm, adjusting intravenous insulin infusion rates according to blood glucose levels. A suggested algorithm is presented in Table 8–3.

CURRENT APPROACHES TO REVASCULARIZATION DECISIONS

In Figure 8–14, we present an integrated and comprehensive approach to making revascularization decisions in the current era. As mentioned in the introduction to this chapter, there are three broad indications for coronary revascularization (1) relief of symptoms and improvement in quality of life; (2) improvement of long-term prognosis (i.e., reduction in the risk of premature death); and (3) prevention of nonfatal events such as MI, congestive heart failure and/or ventricular arrhythmias. It should be recognized that although both PCI and CABG are highly effective in relieving symptoms, only CABG has been definitively shown to improve prognosis in stable CAD, and even then only for the highest risk of anatomical subsets of patients such as those with left main CAD or severe triple-vessel disease, particularly with decreased left ventricular function. Neither procedure has been shown to

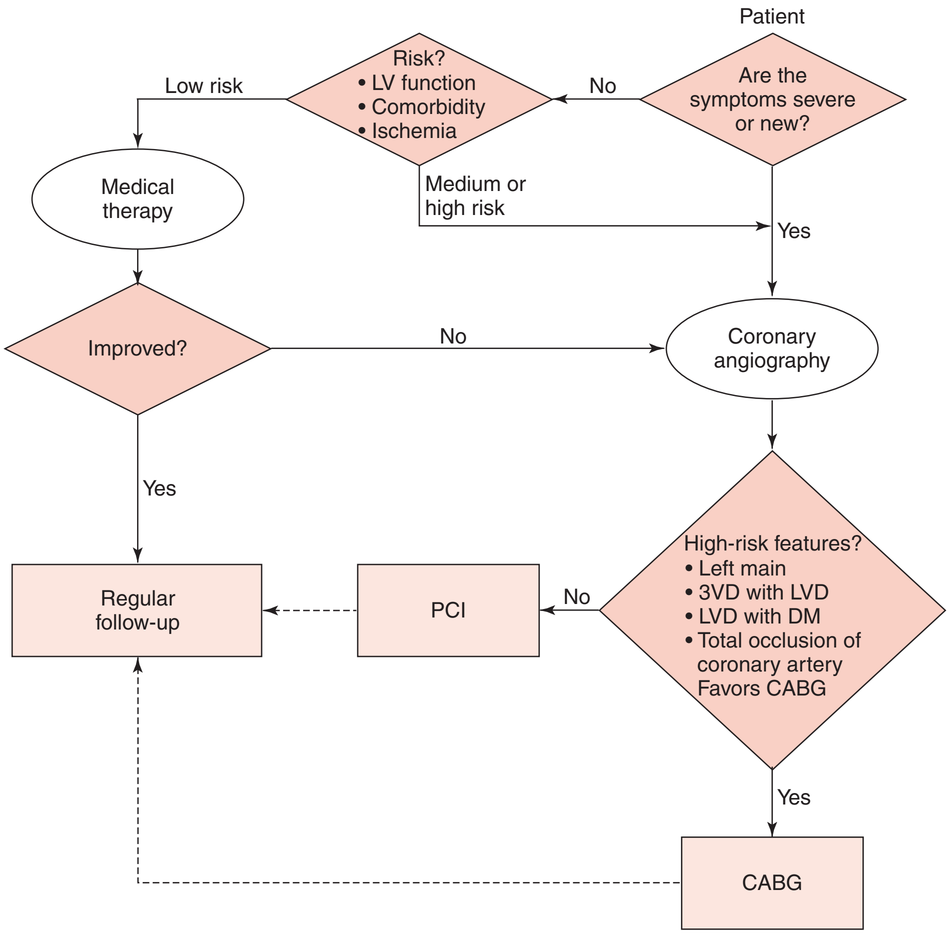


Figure 8–14 A risk-based approach to the management of patients with suspected coronary artery disease. Central to this approach is the ability to develop an estimate of cardiovascular risk based on standard clinical criteria including age, left ventricular function, extent of myocardial ischemia, and medical comorbidities. Low risk can be defined as an estimated annual mortality of <1%, medium risk 1% to 5%, high risk >5%. Various clinical risk scores are available that incorporate clinical and functional information. In general, patients with normal left ventricular function and mild ischemia in the territory of only one coronary artery will have a low annual risk. Regular follow-up entails implementation of aggressive secondary preventive efforts and periodic surveillance for recurrent symptoms or ischemia. CABG, coronary artery bypass graft; DM, diabetes mellitus; LVD, left ventricular dysfunction; 3VD, three-vessel disease; PCI, percutaneous coronary intervention;. (Adapted from Gibbons RJ, Abrams J, Chatterjee K, et al: ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—Summary article: A report of the ACC/AHA Task Force on Practice Guidelines. J Am Coll Cardiol 2003;41:159-68 and Miller TD, Roger VL, Hodge DO, Gibbons RJ: A simple clinical score accurately predicts outcome in a community-based population undergoing stress testing. Am J Med 2005;118:866-72, with permission.)

prevent MI, likely caused by the initial risk of periprocedural myocardial necrosis. In acute presentations, only PCI has been validated in randomized trials for the treatment of UA/NSTEMI.

Revascularization decisions are perhaps most straightforward in acute presentations of ischemic heart disease, whereby patients presenting with UA/NSTEMI should be triaged to hospitals with angiography facilities and undergo early (generally within 24 to 72 hours) coronary angiography.[65,115] Patients presenting with STEMI who can undergo PCI in a timely fashion by skilled operators should undergo immediate coronary angiography with a view to percutaneous revascularization and reperfusion of the infarct-related artery.[65] Should left main CAD or severe multivessel disease be encountered, then subsequent revascularization can be individualized based on each patient's circumstances.[30]

In chronic ischemic heart disease, the situation is more complex, and a rigorous review of the indications and goals of revascularization with the patient and his or her family is necessary. For example, most elderly patients will require revascularization procedures for improvement of quality of life, and long-term prognosis, although important, may be a lesser concern. A younger patient may require revascularization for improving prognosis even in the absence of significant symptoms. These indications should be clearly discussed with the patient before undertaking any revascularization procedure, and the patient's expectations of the effectiveness of the procedure should also be carefully reviewed (e.g., many deconditioned patients may not experience a marked improvement in exercise tolerance or energy unless they are also willing to undertake lifestyle modifications in conjunction with the revascularization procedure).

To allow selection of the most appropriate revascularization method, a detailed assessment of coronary artery anatomy and regional and global left ventricular function is mandatory. Coronary angiography in an accredited and quality-controlled laboratory, possibly supplemented with intravascular ultrasound or coronary physiological measurements, is required for precise anatomic delineation of the degree and extent of CAD. Particular attention to left main coronary artery involvement, the presence or absence of chronic total occlusions, or other complex anatomical subsets such as bifurcation lesions, osteal lesions, and calcified lesions is required. Left ventricular function is the most important determinant of acute and long-term prognosis after revascularization, and either noninvasive or invasive assessments of left ventricular function in conjunction with coronary artery anatomy are necessary. These measures will often have been supplemented by noninvasive assessment of myocardial ischemia, either by perfusion scan or direct visualization with echocardiography. Thus, a comprehensive evaluation of the patient as a candidate for revascularization includes an assessment of symptoms, myocardial ischemia, left ventricular function, and coronary artery anatomy.

In addition to these cardiac factors, a thorough assessment of systemic comorbidities that influence both short- and long-term risks is also needed. In particular, the presence of cerebrovascular disease, diabetes mellitus, peripheral vascular disease, and chronic renal disease all significantly increase the risk of periprocedural complications, as well as portend a poorer long-term prognosis. The next step in patient evaluation requires a technical evaluation of the various modes of revascularization that can be offered. Factors such as the presence of complex lesions or poor distal vessels may influence the selection of one modality versus the other. For example, an unapproachable chronic total occlusion may tilt the balance in favor of complete revascularization with surgery. In general, complete revascularization in chronic CAD is preferable and is associated with improved long-term outcome. Alternatively, the presence of diffuse disease and poor distal vessels with poor outflow may portend a high incidence of periprocedural graft closure and poor prognosis after CABG. A discussion between an experienced interventional cardiologist and cardiovascular surgeon, often in conjunction with the patient's referring physician and family members, will usually lead to the most informed decision-making in these complex circumstances.

The short-term risk of periprocedural complications needs to be balanced against the relative long-term benefits. Because of the greater intensity and more invasive nature of CABG surgery, patients on the one hand frequently are at risk for more periprocedural complications and longer hospital stays with associated costs; on the other hand, complete revascularization and long-term results may be superior in some patient subsets. Ultimately, these considerations need to be carefully weighed in the selection of the revascularization procedure. Patient preference needs to be taken into account because patients will frequently select a less invasive alternative as initial treatment, thereby reserving the more invasive option for a future date. As surgical and interventional techniques along with the associated medical therapy improve, it is increasingly apparent that the techniques are not competitive but in most instances are complementary and that weighing of the foregoing factors will lead to the best decision-making for each patient encountered in clinical practice

LONG-TERM SECONDARY PREVENTION

Patients recovering in the hospital after CABG or PCI are in an ideal environment to initiate secondary prevention measures. Because of the emotional trauma associated with hospitalization and revascularization, patients and families are very receptive to educational measures directed at secondary prevention. There is also evidence that these initiatives, begun in the hospital, are more likely to be followed after discharge.[120] Moreover, the medical advantages of antiplatelet therapy as well as lipid reduction before invasive procedures in hospital are considerable. The American Heart Association has initiated a program called "Get with the Guidelines" to encourage in-hospital initiation of secondary prevention measures for all patients who have CAD.[121] The American College of Cardiology has also promoted the "Guidelines Applied in Practice" (GAP) program to assist cardiologists and others to improve quality and efficiency of care by giving them practical tools that encourage implementation of guidelines at the point of care.[122] Similar initiatives have also been undertaken by the Society of Thoracic Surgeons as part of its quality improvement program.[2]

Aspirin

All patients with CAD should receive aspirin (81mg to 162 mg) indefinitely.[123] This can be commenced within 6 hours of CABG and may be given through a nasogastric tube if the patient is not yet extubated. Mangano and colleagues[124] studied 5022 patients in a global registry who survived CABG. Aspirin therapy begun within 48 hours after surgery resulted in a 60% lower death rate at 30 days, as well as decreased rates of MI, stroke, renal failure, and bowel infarction. It is likely that these effects are mediated by both the anti-inflammatory and antithrombotic actions of aspirin.[125] Bleeding complications were also lower in the aspirin-treated group. The most appropriate dose of aspirin is not known. However, the lower dose of aspirin (81 mg) will have fewer side effects and is most probably equally as effective as higher doses.

Cholesterol Reduction

The need to reduce serum lipids in patients with CAD is well accepted. There are accumulating data that statins may also have a beneficial effect on bypass grafts in preventing or slowing the development of graft atherosclerosis and that these benefits may be independent of the starting and resulting LDL-C levels.[126-129] In the Post Coronary Artery Bypass Graft (Post CABG) Trial, aggressive lowering of LDL cholesterol to 60 to 85 mg/dL with lovastatin (up to 80 mg daily) resulted in a significant reduction in graft atherosclerosis and occlusion compared with the group of patients who had only moderate reduction of LDL cholesterol (130 to 140 mg/dL).[127] The early phase of the trial lacked statistical power to study clinical events. There was, however, a 29% reduction in revascularization procedures in the aggressively treated group compared with the moderately treated group. In

a longer term follow-up of 7.5 years, cardiovascular mortality rates and the rate of nonfatal MI or stroke were reduced by 24% in the aggressively treated group (P = 0.001).[128] In the CARE (Cholesterol and Recurrent Events) trial, patients who had a documented MI were randomized to treatment with either placebo or pravastatin.[129] In those patients who were revascularized, treatment with pravastatin led to significant reduction in fatal and nonfatal MI, repeat revascularization, and stroke. These effects were seen in both PCI and CABG patients.

Almost all patients who have undergone PCI and/or CABG should be discharged from the hospital on a HMG-CoA reductase inhibitor (statin) therapy unless their LDL-C level is <70 mg/dL with nonpharmacological treatment. Although the optimal level of LDL-C for patients who have CAD and who have undergone revascularization (either PCI and/or CABG) is not known, other benefits of statins may include their anti-inflammatory and antithrombotic effects.[126] Lipid levels and AST assays should be rechecked in 6 weeks after commencing statins.

β-Blockers

Trials have demonstrated significant reduction in mortality (23% at 5 years) in patients treated long term with β-blockers after MI.[130] Because 50% to 60% of patients undergoing revascularization have had a previous MI, the majority of these patients should be treated with a β-blocker postoperatively. In addition, β-blockers are useful in treating postoperative atrial fibrillation as well as hypertension. Preferred β-blockers include metoprolol or carvedilol.

ACE Inhibitors

A number of trials that randomized more than 100,000 patients have shown a clear benefit of angiotensin-converting enzyme (ACE) inhibitors in patients with CAD and impaired left ventricular function.[131] We recommend ACE inhibitors, if possible, for all patients who have undergone CABG and/or PCI and who have an EF of <40%. Because of issues of postural hypotension in the early postoperative period when combining ACE inhibitors with a β-blocker, use of these medications may need to be individualized depending on clinical circumstances (e.g., need to control atrial fibrillation, poor left ventricular function, recent MI, diabetes). Nevertheless, high-risk patients should be discharged, if possible, on ACE inhibitors as well as β-blockers.

Lifestyle Changes

All patients should be counseled regarding smoking cessation, diet, and exercise. Patients who continue to smoke after CABG have a greater risk of death and repeat revascularization compared with patients who quit smoking.[131,132] At 5 years, the survival benefit for those who have stopped smoking may be as high as 14%.[133,134] Patients are encouraged to enroll in a cardiac rehabilitation program based on exercise training, smoking cessation, diet, lipid management, psychosocial management, and occupational assessment. Programs based on exercise therapy have been shown to reduce subsequent cardiac morbidity and mortality over the ensuing 5 to 10 years.[135]

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Primary Prevention of Ischemic Heart Disease

Judith Meadows, Jacqueline Suk Danik, and Michelle A. Albert

CHAPTER CONTENTS

Cardiovascular disease (CVD) is the leading cause of death worldwide resulting in more than 17 million deaths.[1] In the United States alone, coronary artery disease affects more than 12 million Americans.[2] Over the last 3 decades, the mortality from CVD has declined progressively in all race/ethnic and gender groups, a trend that has begun to level off (Fig. 9–1).[3,4] Advances in the detection and treatment of CVD have resulted in the noted decline and longer life expectancy enjoyed by many in the developed world. Primary prevention focusing on identification and treatment of hyperlipidemia and hypertension, as well as the use of aspirin, have contributed considerably to improvements in outcome.

However, significant challenges remain in combating the CVD crisis—including the differences in morbidity and mortality by race/ethnic group; gender and socioeconomic status; the burgeoning obesity epidemic in the developed as well as in many parts of the developing world; the need to better identify and treat persons to reach current guideline goals; and the continuing escalating cost of care. Risk communication and physician and public understanding of and compliance with recommended treatment guidelines are other major challenges in reducing coronary heart disease (CHD), morbidity, and mortality. For example, because CHD scoring algorithms generally do not take into account an individual's relative risk of CHD compared with others in his or her age category, an individual who is 35 years of age who might be at moderate to high risk for CHD for his or her age category could miss the opportunity for primary prevention because he or she is considered to have a low 10-year absolute risk of CHD—resulting in physicians not adequately being able to communicate risk.[5]

RISK DETERMINATION

The most critical step toward decreasing CVD burden involves early identification, monitoring, and treatment of at-risk individuals. The goal of primary prevention is to prevent the development of disease in an asymptomatic person via the early identification and treatment of risk factors for cardiovascular disease. However, an essential step in the latter involves adequate risk assessment. *Absolute risk* of CVD is the risk of developing CVD during a given period of time (typically a period of 10 years), whereas *attributable risk* refers to the difference in the incidence of CVD between person(s) who have been exposed and have not been exposed to a cardiovascular risk factor(s). Traditionally, risk stratification for CHD has used algorithms such as the Framingham Cardiovascular Risk Score (Fig. 9–2)[6] and the European Society of Cardiology Coronary Risk Chart (Fig. 9–3).[7] Both scoring systems estimate an individual's absolute 10-year risk of a CHD event based on gender. Traditional risk factors for CHD such as age, smoking status, presence or absence of diabetes, total cholesterol level (or low density cholesterol level) and systolic blood pressure are included in both scoring modules; diastolic blood pressure and high density lipoprotein are included in the Framingham risk equation but not in the European scoring system. Persons who have an absolute risk of CHD greater than 20% are considered high risk and are candidates for intensive risk reduction through behavioral and drug treatment. Intermediate risk defines persons at 10% to 20% absolute risk of CHD, a group in which safe, cost-effective interventions are recommended. Low-risk individuals have less than a 10% absolute 10-year risk of CHD. However, the usefulness of these scoring systems in non-white populations has come under scrutiny particularly in the United States. Additionally, the ascribed categories of low (<10%) and high (>20%) still leaves a large number of intermediate risk individuals who might also benefit from early intervention. It is estimated that intermediate risk comprises 40% of the U.S. population.[8]

The traditional risk factors for CHD comprise both modifiable and nonmodifiable components. Modifiable risk factors

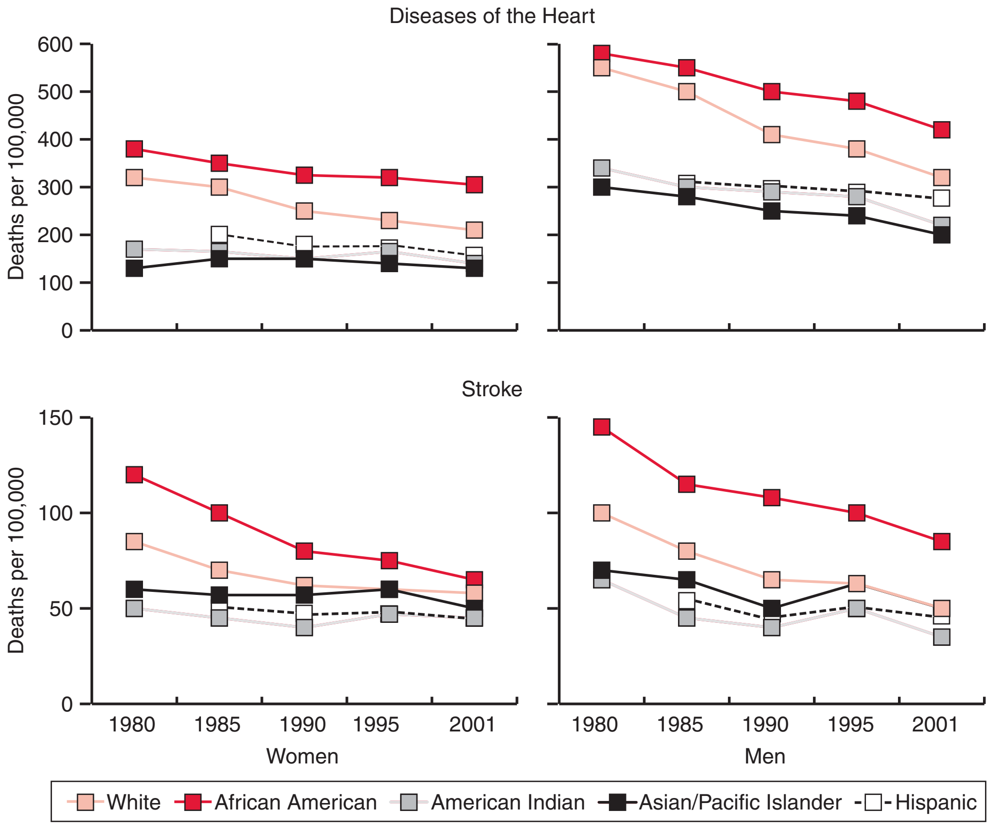

Figure 9–1 Death rates for diseases of the heart and stroke by race/ethnicity and sex in the United States, 1980 to 2001: Age adjusted to the 2000 U.S. population. (From Mensah GA, Mokdad AH, Ford ES, et al: State of disparities in cardiovascular health in the United States. Circulation 2005;111[10]: 1233-1241.)

include dyslipidemia, diabetes, smoking, hypertension, diet, and lack of exercise, whereas nonmodifiable factors include age and family history of CHD. Other factors that contribute significantly to CHD risk include postmenopausal status among women, psychosocial and socioeconomic factors. Over the past few years, debate has ensued regarding the prevalence of conventional risk factors in patients who develop CHD and has led to the proliferation of research related to nontraditional risk factors of CHD.[9,10] Because the pathophysiology of CHD involves the interaction of lipids and inflammation, molecular, hemostatic, and inflammatory markers such as C-reactive protein (CRP), serum amyloid A (SAA), vascular and cellular adhesion molecules, soluble CD40 ligand, fibrinogen, lipoprotein (a), homocysteine, lipoprotein phospholipase A2, and plasminogen activator inhibitor 1 (PAI-1) have emerged as novel risk predictors of CHD.[11,12]

Traditional as well as nontraditional risk indicators of CHD demonstrate a graded CHD risk effect. Much of the evidence to support these relationships has been derived from prospective epidemiologic cohort studies. Besides prospective epidemiologic cohorts, other study designs include cross-sectional, prospective, retrospective cohort, case-control, and randomized clinical trials. Table 9–1 demonstrates a listing of common study designs used in CHD research. Measurement tools to detect subclinical atherosclerosis such as carotid ultrasonography, electron beam computed tomography, and exercise stress testing identify subclinical CHD in clinical trials and population-based cohorts. However, these tests are not incorporated into cardiovascular risk score analyses, and the ability of these tools to determine adequately total vascular disease burden is limited.

DYSLIPIDEMIA

The causal relationship between dyslipidemia and CHD events/mortality has been confirmed in large, randomized controlled trials of primary prevention with HMG Co-A reductase inhibitors.[13-17] A large body of evidence in primary and secondary prevention demonstrates that statin therapy reduced CHD events by 31% and all-cause mortality by 21% (Table 9–2).[18-20] Trials with fibrates and cholestyramine have demonstrated both positive[21,22] and negative[23] results for primary prevention of CHD in patients with hypercholesterolemia.

LDL cholesterol is considered the primary atherogenic factor and is the current focus for primary prevention of CHD.[24] The Lipid Research Clinics Prevalence Study showed that 10-year mortality is associated with high LDL cholesterol in patients with and without CHD.[25] Similarly, several studies have demonstrated that LDL lowering reduces CHD risk and CHD mortality.[26] The West of Scotland Coronary Prevention Study (WOSCOPS) is a large-scale primary prevention study that demonstrated a decrease in CHD events in men with hypercholesterolemia who were administered lipid-lowering therapy to reduce LDL.[17] The greatest benefit of pravastatin therapy was seen in the highest risk group with the number needed to treat of 17 patients over 5 years to prevent one death. The number needed to treat in the low-risk group was 66 individuals for 5 years to prevent one death. The absolute benefit in WOSCOPS for primary prevention was three times lower than that seen for secondary prevention in the 4S trial.[27]

In prospective trials of LDL lowering for primary prevention of CHD, there does not appear to be a lower

Figure 9–2 Coronary heart disease (CHD) score sheet for calculating 10-year CHD risk according to age, total cholesterol (TC) (or low-density lipoprotein cholesterol [LDL-C]), high-density lipoprotein cholesterol (HDL-C), blood pressure, diabetes, and smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Score sheet for men based on the Framingham experience in men 30 to 74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC of 160 to 199 mg/dL (or LDL of 100 to 129 mg/dL), HDL-C of 45 mg/dL, no diabetes, and no smoking.

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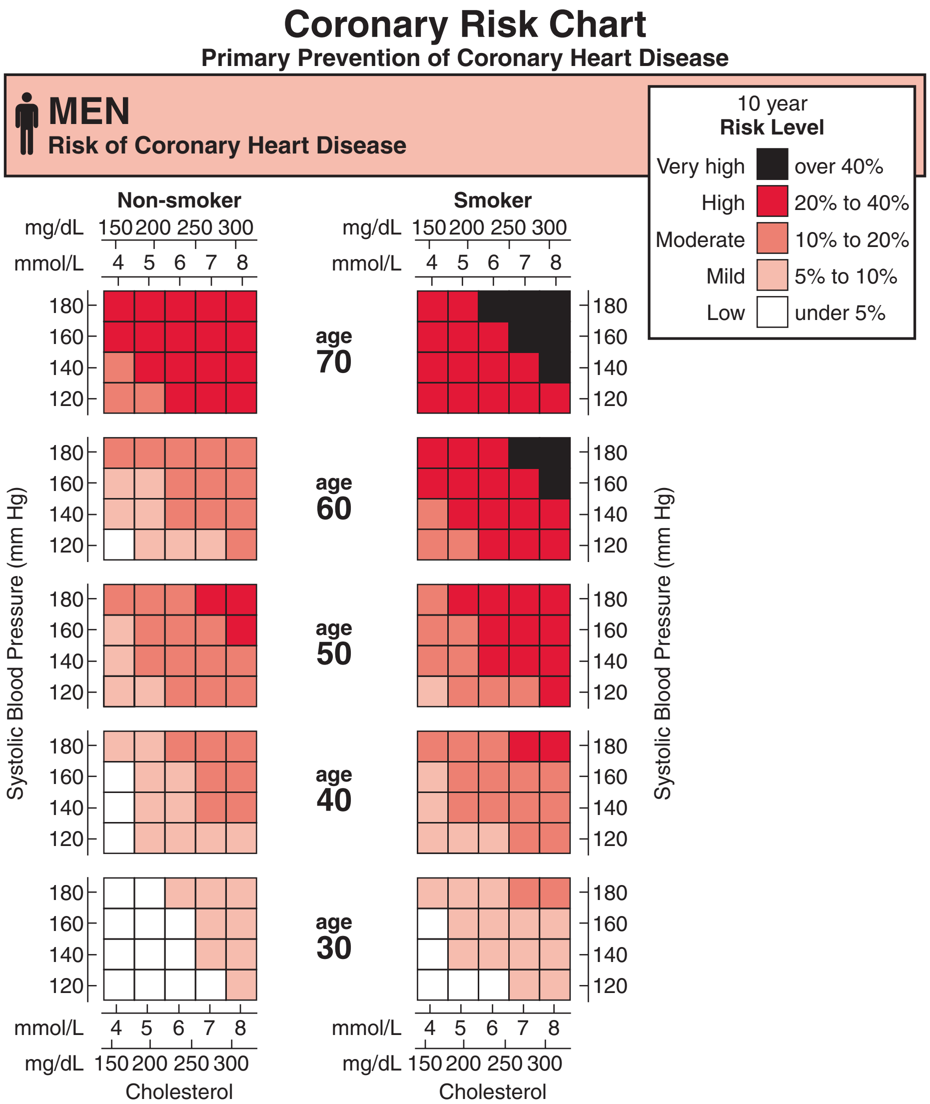
Figure 9–2 *Continued.* Score sheet for women based on the Framingham experience in women 30 to 74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC of 160 to 199 mg/dL (or LDL of 100 to 129 mg/dL), HDL-C of 55 mg/dL, no diabetes, and no smoking. Pts = points. (From Wilson PW, D'Agostino RB, Levy D, et al: Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47. By permission of the American Heart Association, Inc.)



How to Use the Coronary Risk Chart for Primary Prevention

The chart is for estimating coronary heart disease (CHD) risk for individuals who have not developed symptomatic CHD or other atherosclerotic disease. Patients with CHD are already at high risk and require intensive lifestyle intervention and, as necessary, drug therapies to achieve risk factor goals.

- **To estimate a person's absolute 10 year risk of a CHD event,** find the table for their gender, smoking status, and age. Within the table, find the cell nearest to their systolic blood pressure (mm Hg) and total cholesterol (mmol/L or mg/dL).
- **The effect of lifetime exposure to risk factors** can be seen by following the table upwards. This can be used when advising younger people.
- **High-risk individuals** are defined as those whose 10-year CHD risk exceeds 20% or will exceed 20% if projected to age 60.

A

Figure 9–3 Risk assessment tool for men *(A)* and women *(B)* devised by a European task force on coronary prevention using cholesterol levels, blood pressure, and smoking status. (From Prevention of coronary heart disease in clinical practice: Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. Eur Heart J 1998;19:1434-503.)

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threshold of LDL below which CHD benefit is lost. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a trial for primary prevention of CHD in patients with low HDL cholesterol (average total cholesterol 221 mg/dL and LDL cholesterol 150 mg/dL) randomized to a low fat/low total cholesterol diet and lovastatin or placebo.[15] Lovastatin was associated with a 37% reduction in CHD events at 5.2 years. The benefit of LDL lowering in primary prevention extended to patients with normal LDL cholesterol levels. In the WOSCOPS, AFCAPS/TexCAPS, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) trial of hypertensive individuals, and the Collaborative Atorvastatin Diabetes Study (CARDS) trial of diabetics, individuals with multiple cardiac risk factors derived the greatest benefit from lipid reduction.[28,29] Furthermore, angiographic trials report that statin therapy is associated

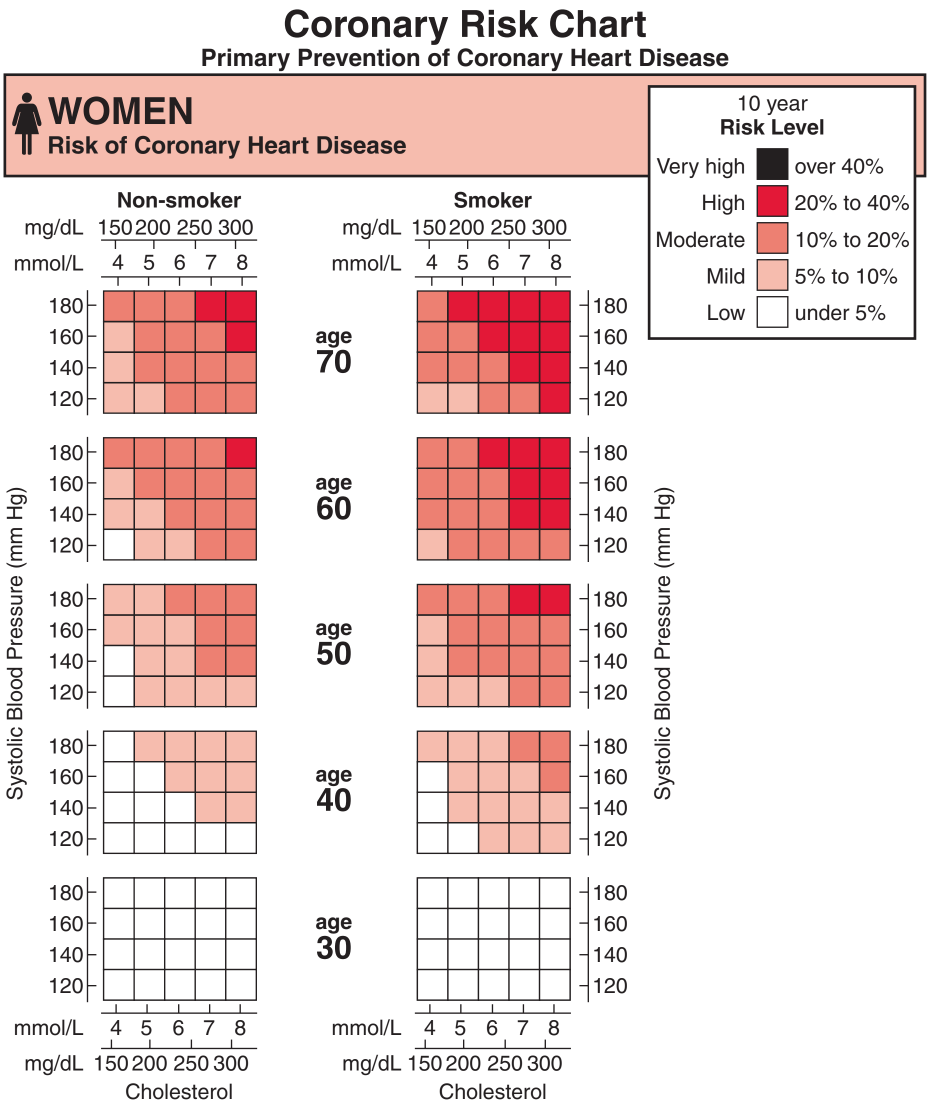

Figure 9–3 *Continued.*

- **CHD risk is higher than indicated in the chart for those with**
  - Familial hyperlipidemia
  - Diabetes: risk is approximately doubled in men and more than doubled in women
  - Those with a family history of premature cardiovascular disease
  - Those with low HDL cholesterol. These tables assume HDL cholesterol to be 1.0 mmol/L (39 mg/dL) in men and 1.1 (43) in women
  - Those with raised triglyceride levels >2.0 mmol/L (>180 mg/dL)
  - As the person approaches the next age category
- **To find a person's relative risk,** compare their risk category with those for other people of the same age. The absolute risk shown here may not apply to all populations, especially those with a low CHD incidence. Relative risk is likely to apply to most populations.
- **The effect of changing cholesterol,** smoking status, or blood pressure can be read from the chart.

B

with retarded progression and regression of atherosclerotic lesions.[30,31] Statins may also provide benefit beyond lesion regression and confer antithrombotic and anti-inflammatory effects.[32]

Optimal LDL cholesterol levels for both men and women are defined by the epidemiological, retrospective, and prospective trials. In the ARIC study, LDL cholesterol levels greater than 118 mg/dL were associated with an age-adjusted increase in CHD of 42% in men and 37% in women.[33] An HDL of 1 SD above the mean (40 mg/dL in men and 51 mg/dL in women) was associated with a 36% decrease in CHD risk among men and a 31% decrease in CHD risk among women. Prediction of CHD risk was not enhanced by HDL subtypes. Also an independent predictor of CHD in women, triglycerides elevated 1 SD above a mean triglyceride of 115 mg/dL was associated with a 31% increase in CHD risk. Additionally,

Table 9–1 Common Study Designs in Coronary Heart Disease Research

Study Type	Goals	Subjects	Advantages	Disadvantages
Experimental				
Randomized clinical trial	To evaluate potential treatment for a disease. To identify a preventive of disease sequelae. To prevent disease in those at risk.	Patients with disease Persons at risk of disease	More equal/balanced distribution of potential confounders Risks and benefits of given exposure/intervention can be evaluated.	Can be expensive
Field trial: Community Intervention Trial Cluster Randomized Field Trial	Intervention implemented on a community-wide basis Treatment assigned randomly to group of participants	Disease-free subjects		Visit subject in the field or subjects come to a central locale Can be expensive when used to study extremely common or serious disease
Nonexperimental				
Cohort study (can be follow-up or incidence study)	To identify and follow a population to evaluate disease	Compares different exposure groups who are initially disease free	Can establish incidence directly. Minimizes recall and other biases that may occur if the outcome is already known. Can assess the relation between an exposure and many diseases.	Many more subjects must be enrolled than will experience the outcome of interest. Expensive, due to high cost of studying many people over long periods of time. Cannot be used to investigate rare diseases. A long time is required for results to emerge.
Case-control study	To determine the contribution of a risk factor within a source population (relative effect measure). To evaluate new risk factors.	Samples according to the outcome of individuals in a population. Controls must be sampled independently of their exposure status.	Efficient Investigates rare diseases	Selection and recall bias
Cross-sectional study	To generate a hypothesis	Subjects represent all persons in a population (or a representative sample) at time of ascertainment. Both exposure and disease are assessed at same time. Includes those with and without disease.		Cannot control for confounding factors. Cannot distinguish whether exposure preceded disease or if disease affected exposure (i.e., current exposure may be unrelated to current disease). Over-represents cases with long duration and under-represents those with short duration of disease.

Adapted and modified from Rothman KJ, Greenland S: Modern epidemiology, 2nd ed. Lippincott Williams and Williams, Philadelphia, 1998.

Table 9–2 Primary and Secondary Prevention Studies Using Statins

Study, *n* (% Women)	Intervention	Baseline LDL, mg/dL,	% LDL Reduction	On-Trial LDL,* mg/dL	% Reduction in Total Mortality	% Reduction in Coronary Events	% Reduction in CABG and PTCA	NNT
Secondary-Prevention trials								
4S, 4444 (19)	Simvastatin 20-40 mg/d	188	35	120	30 ($P = 0.003$)	34 ($P < 0.0001$)	37 ($P < 0.0001$)	15
CARE, 4159 (14)	Pravastatin 40 mg/d	139	32	95	9 (P = NS)	24 ($P = 0.003$)	27 ($P < 0.001$)	33
LIPID, 9014 (17)	Pravastatin 40 mg/d	150	25	113	22 ($P < 0.0001$)	24 ($P < 0.0001$)	22† ($P < 0.0001$)	28
Primary-Prevention trials								
WOSCOPS, 6595 (0)	Pravastatin 40 mg/d	192	26	142	22 ($P = 0.051$)	31 ($P < 0.001$)	37 ($P < 0.009$)	42
AFCAPS/TexCAPS, 6605 (15)	Lovastatin 20-40 mg/d	150	25	113	0 (P = NS)	37 ($P < 0.001$)	33 ($P < 0.001$)	24

*On-trial LDL-C values are calculated from published data.
†Results for CABG; the need for PTCA was reduced by 19% (P = 0.024). NNT indicates number needed to treat to prevent one major coronary event (100/absolute risk reduction).
From Maron, Fazio DJ, Linton MF: Circulation 2000;101:207-13.

Lp(a) elevation of 1 SD above the mean of 8.7 mg/dL in men and 11 mg/dL in women was associated with a 15% and 17% increase CHD risk among men and women, respectively. Clustering of multiple CHD risk factors also heightened the risk of CHD.

Screening for Dyslipidemia

Based on findings from large, randomized clinical trials, the National Cholesterol Education Program (NCEP) issued the third Adult Treatment Panel (ATP III) report in 2001 offering guidelines to reduce the incidence of dyslipidemia.[24] NCEP/ATP III recommends that all adults older than 20 years obtain a fasting lipoprotein panel every 5 years. Total cholesterol levels vary by 4% to 11% due to stress, minor illness, and posture.[34] The American College of Physicians recommends screening of men aged 35 to 65 years and women aged 45 to 65 years.[35] In addition, the United States Preventive Services Task Force recommends routine screening of adults between 20 to 35 years if they have other CHD risk factors.[36]

The ATP III guidelines recommend treatment goals based on three CHD risk categories.[24] (Tables 9–3 and 9–4). High risk includes individuals with preexisting CHD or CHD risk equivalents and includes a 10-year CHD mortality of greater than 20%. CHD risk equivalents include peripheral vascular disease, abdominal aortic aneurysm, symptomatic carotid disease, and diabetes mellitus. Individuals with LDL cholesterol greater than 100 mg/dL should initiate therapeutic lifestyle changes. Individuals with LDL cholesterol greater than 130 mg/dL should be placed on lipid-lowering medications.

Treatment Recommendations for Dyslipidemia Categories

High-risk patients with elevated triglycerides or low HDL cholesterol levels also benefit from therapy directed at these specific dyslipidemias. Although ATP III guidelines do not mandate drug therapy when LDL is less than 129 mg/dL, high-risk patients appear to benefit from an LDL cholesterol goal <70 mg/dL. Since the publication of ATP III guidelines, four randomized trials (HPS, PROSPER, ASCOT-LLA, and PROVE IT-TIMI 22) have recommended reduced treatment thresholds for high-risk patients.[29,37-39]

ATP III defines intermediate risk as the presence of two or more CHD risk factors and a 10-year CHD mortality of less than 20%. Intermediate risk patients should achieve a goal LDL cholesterol of less than 130 mg/dL through lifestyle changes. If lifestyle changes fail to achieve LDL lowering to 130 mg/dL or if the initial LDL cholesterol is greater than 160 mg/dL, drug therapy should be initiated. Finally, ATP III defines low risk as one or no risk factors and a 10-year CHD mortality of less than 10%. However, some argue that some individuals in this category may in fact be intermediate risk. The goal LDL for low-risk individuals is less than 160 mg/dL. If the LDL cholesterol remains greater than 190 mg/dL after therapeutic lifestyle changes, LDL lowering medications may be prescribed. An HDL cholesterol greater than 60 mg/dL is considered protective against CHD. Figure 9–4 outlines the treatment algorithms for elevated LDL cholesterol.

NCEP/ATP III offers recommendations for cholesterol reduction with lifestyle/pharmacologic intervention based on individual risk profile and LDL cholesterol level. The first-line strategy is lifestyle intervention (see Fig. 9–4A). Diet should include less than 7% of calories from saturated fat, less than 200 mg cholesterol per day, 55% of daily calories from carbohydrates, 15% of daily calories from protein, 10% of daily calories from polyunsaturated fat, and 20% of daily calories from monounsaturated fat. In addition, patients should pursue weight reduction and physical exercise. If LDL cholesterol goal is not achieved within 6 weeks, plant stanols/sterols and fiber should be added to the diet. Drug therapy should be initiated if LDL goal is not met within another 6 weeks (see Fig. 9–4B). The European Society of

Table 9–3 ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol	
<100	Optimal
100-129	Near or above optimal
130-159	Borderline high
160-169	High
Cigarette smoking	
Hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication)	
Low HDL cholesterol (<40 mg/dL)	
Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)	
Age (men ≥45 years; women ≥55 years)	

Diabetes is regarded as a coronary heart disease (CHD) risk equivalent; LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; HDL cholesterol >60 mg/dL counts as a "negative" risk factor; its presence removes a risk factor.
From NCEP/ATP. JAMA 2001;285:2486-2497.

Table 9–4 LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)*
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor†	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

*Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL; e.g., nicotinic acid or fibrate. Clinical judgment also may call for differing drug therapy in this subcategory.
†Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary. LDL: low-density lipoprotein; CHD, coronary heart disease.
From NCEP/ATP. JAMA 2001;285:2486-2497.

Cardiology (ESC) recommends initial lifestyle modifications for all risk categories before the use of medications.[7]

Although both the NCEP/ATP III and ECS recommend lifestyle changes as first-line therapy, the evidence of CHD benefit is limited. In the United Kingdom Lipid Clinics program, among individuals treated with dietary changes—60% had mean weight reduction of 1.8%, which was associated with a 5% to 7% reduction in total cholesterol and LDL cholesterol.[40] In another study of patients with low HDL and elevated LDL cholesterol who were randomized to exercise, low fat/low cholesterol diet, exercise plus diet, or usual care, those treated with exercise plus low fat/low cholesterol diet had a significant reduction in LDL (14.5±22.2 mg/dL in women, 20.0±17.3 mg/dL in men) compared with other groups. Significant LDL cholesterol reduction was not achieved in the diet alone group.[41]

Despite good evidence of the cardiovascular benefit of cholesterol reduction, the NHANES study described suboptimal awareness, lipid panel screening, and control of dyslipidemia. Only 20% of U.S. adults have had their serum cholesterol evaluated.[42] Of individuals with total cholesterol greater than 200 mg/dL, 69.5% have undergone lipid panel testing; only 35% of this group were aware of their diagnosis and only 12% were treated for elevated cholesterol.[43]

TRIGLYCERIDES AND HDL-C

While total cholesterol and LDL cholesterol are the primary targets of the NCEP/ATP III guidelines, other atherogenic dyslipidemias confer heightened cardiovascular risk. In a meta-analysis of prospective population studies, an 88 mg/dL increase in triglyceride level independently conferred a 14% and 37% increased risk of CHD in men and women, respectively.[44] The increased CHD risk of hypertriglyceridemia is independent of HDL concentration.[45,46]

Low serum HDL, which often accompanies elevated triglycerides, is another important risk factor for CHD. In the Framingham Heart Study, each 5 mg/dL decrease in HDL from median values was associated with a 25% increase in the risk of myocardial infarction.[47] Also, an analysis of four prospective U.S. trials demonstrated that each 1 mg increase in HDL was associated with a 2% decrease in CHD risk among men and a 3% decrease in CHD risk among women.[48] There are no prospective trial data of primary prevention of CHD with fibrates in individuals with low HDL cholesterol, but post-hoc analyses of fibrate trials show reduction in CHD risk, especially among diabetics and those with the metabolic syndrome.[49] The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group (VA-HIT) assessed

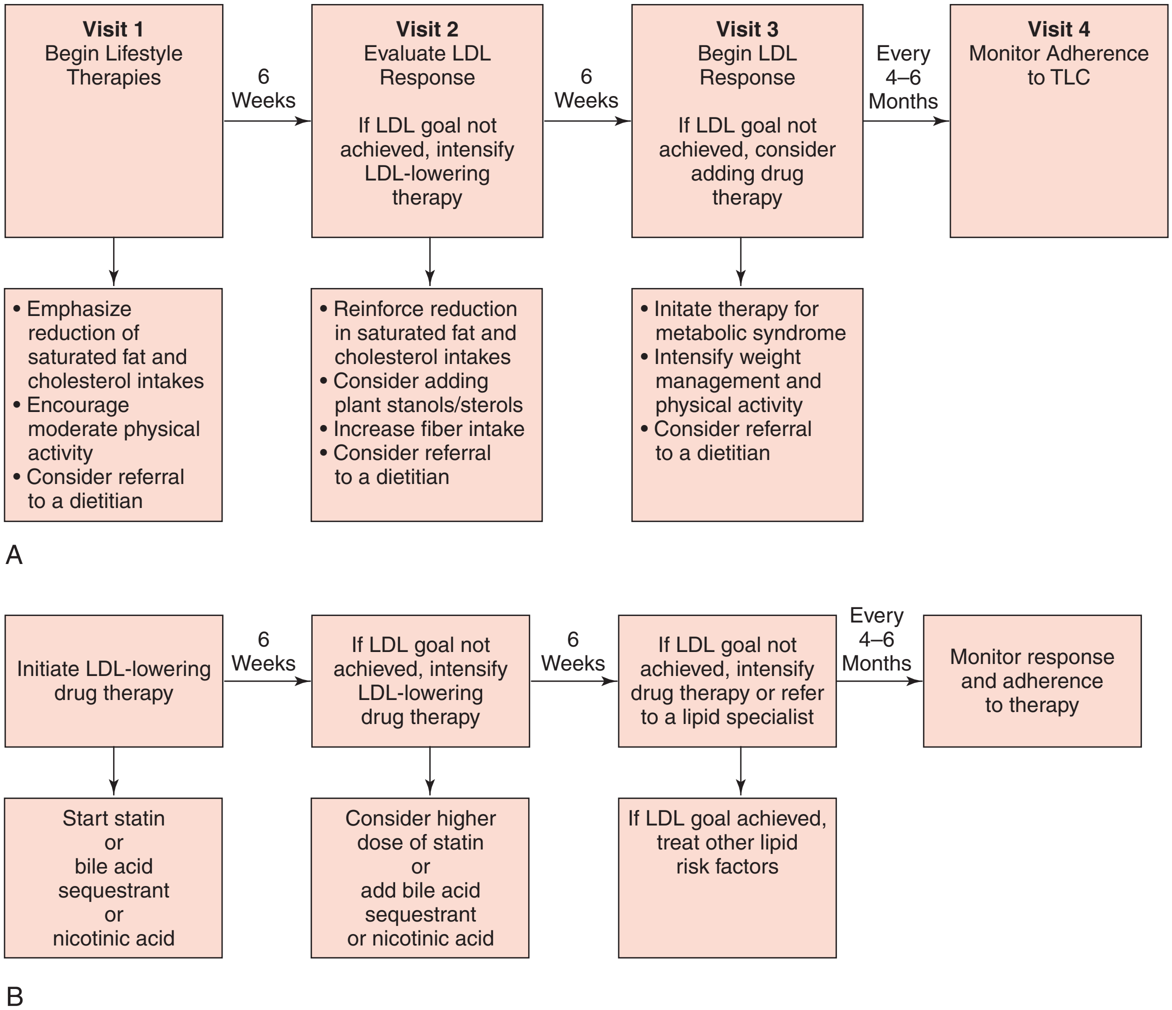

Figure 9–4 **A,** Model of steps in therapeutic lifestyle changes (TLC). **B,** Progression of drug therapy in primary prevention. LDL, low-density lipoprotein. (From Executive Summary of The Third Report of The National Cholesterol Education Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III]. JAMA 2001;285:2486-97.)

the role of gemfibrozil in the secondary prevention of CHD in men with CHD and isolated low HDL cholesterol (mean 32 mg/dL). Gemfibrozil was associated with a 7.5% increase in HDL cholesterol and a 22% reduction in CHD death or nonfatal MI.[50] Although all fibrates can be used in combination with statins for management of dyslipidemia, fenofibrate in combination with a statin has not been associated with a substantial increase in myopathy risk.[51] Nicotinic acid has also been shown to increase HDL cholesterol and reduce CHD risk when used alone and in combination with statins.[52]

APOLIPOPROTEINS

Although LDL is the primary target of lipid lowering strategies, some data support the measurement of apolipoprotein-B and LDL particle concentrations. Small LDL particles or small core cholesterol content confer a heightened CHD risk than merely indicated by LDL concentration.[53] In the Familial Atherosclerosis Treatment Study (FATS) and the Women's Health Study (WHS), changes in LDL buoyancy and particle size were important predictors of CHD.[54,55] In diabetic patients, small dense LDL levels had a significant association with CHD progression independent of LDL cholesterol, apolipoprotein B, and triglyceride levels.[56] New measurements of APO-B and APO A-1 assess total number of atherogenic (LDL, VLDL, IDL) and anti-atherogenic particles (HDL), respectively. Some studies have demonstrated that high APO-B and low APO A-1 are important predictors of CHD risk.[33,57,58] The Apolipoprotein-related MOrtality RISk (AMORIS) and the AFCAPS/TexCAPS studies both concluded that APO-B was a stronger predictor of coronary events than was LDL cholesterol.[59,33]

Another lipid target is the total cholesterol/HDL ratio; studies indicate that this ratio has a greater predictive value for CHD than LDL cholesterol or total cholesterol.[60,61] In men, a ratio greater than or equal to 6.4 identified a 2% to 14% greater CHD risk than predicted by total cholesterol or LDL alone. In women, a ratio greater than or equal to 5.6 identified a 25% to 45% greater CHD risk than predicted by total cholesterol or LDL alone. A 1 unit decrease in the total cholesterol/HDL ratio was associated with a 53% reduction in

risk of myocardial infarction. In a comparison of the predictive utility of different lipid measures, total cholesterol/HDL and APO-B/APO A-1 ratios (hazard ratios 3.81 and 3.01, respectively) were more predictive of CHD events than non-HDL cholesterol, LDL cholesterol, APO A-1, or APO-B (hazard ratios 2.51, 1.62, 1.75, and 2.50), respectively.[61a] Measurement of apolipoproteins may not add predictive value to standard lipid measurements given the close association of non-HDL cholesterol with APO-B and total cholesterol/HDL ratio with APO-B/APO A-1 ratio.

HYPERTENSION

According to the WHO, hypertension is the single most preventable cause of death. The JNC VII defines hypertension as systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure as greater than or equal to 90 mm Hg, or use of antihypertensive medications.[62] Hypertension is the most common diagnosis in the United States and accounts for 35 million office visits.

An estimated 60 million Americans are hypertensive. The prevalence of hypertension increases as the population ages. In the Framingham Heart Study, among individuals who were 55 years old, more than 50% developed hypertension within the subsequent 10 years.[63] There are an estimated 2 million individuals diagnosed with hypertension each year,[64-66] and worldwide there are 1 billion hypertensive individuals.

Risk factors for the development of hypertension include advanced age, sedentary lifestyle, body-mass index, excess sodium consumption, low dietary potassium, alcohol use, family history of hypertension, and African-American ancestry.[67] Additionally, population studies demonstrate that the prevalence of hypertension is highest in older individuals, non-Hispanic blacks, and females (Fig. 9–5).[68] The designation of prehypertension (SBP 120 to 139 mm Hg/DBP 80 to 89 mm Hg) implies an increased risk for progression to hypertension.[69] Moreover, normal blood pressure (systolic blood pressure 120 to 129 mm Hg, diastolic blood pressure 80 to 89 mm Hg) confers a two to four times increase in risk of developing hypertension than optimal blood pressure (systolic blood pressure less than 120 mm Hg, diastolic blood pressure less than 80 mm Hg).[70]

Epidemiological studies demonstrate a continuous, consistent, linear relationship between blood pressure and cardiovascular disease that is independent of other cardiac risk factors.[69,71] In the INTERHEART study, hypertension accounted for 18% of the population attributable risk for a first myocardial infarction.[57] In The Prospective Studies Trialists' collaboration, a meta-analysis of more than 1 million individuals without a history of coronary heart disease or stroke, each incremental increase in systolic blood pressure of 20 mm Hg, and diastolic blood pressure of 10 mm Hg resulted in the doubling of CHD risk over a blood pressure range of 115/75 to 185/115 mm Hg (Fig. 9–6).[66]

Hypertensive individuals also have a higher prevalence of other atherogenic risk factors such as dyslipidemia, glucose intolerance, obesity, metabolic syndrome, and left ventricular hypertrophy than do normotensive individuals. The coexistence of cardiac risk factors with hypertension lends an additive effect on the relative risk of CHD.[72] Of public health relevance are data from the Medical Research Council (MRC) trial of mild hypertensives. The number needed to treat to prevent one CHD event was 262 over 5 years, and for persons older than 55 years who smoke and have systolic blood pressures greater than 160 mm Hg, the number needed to treat was four over a period of 5 years to prevent one CHD event.[73]

Randomized clinical trials demonstrate that blood pressure reduction is beneficial in reducing morbidity and mortality related to stroke, coronary heart disease, and heart failure.[74] Treatment of hypertension resulted in a reduction in the incidence of cerebrovascular disease by 35% to 40%, of myocardial infarction by 20% to 25%, and of heart failure by greater than 50%.[75] Treatment of mild-to-moderate hypertension is also critical. A meta-analysis of hypertension treatment trials of 37,000 individuals with mild-to-moderate hypertension revealed that, a decrease in diastolic blood pressure of 5 to 6 mm Hg reduced the incidence of myocardial infarction by 14% and total CVD by 42%.[76] The benefit of hypertension treatment has been demonstrated in both primary and

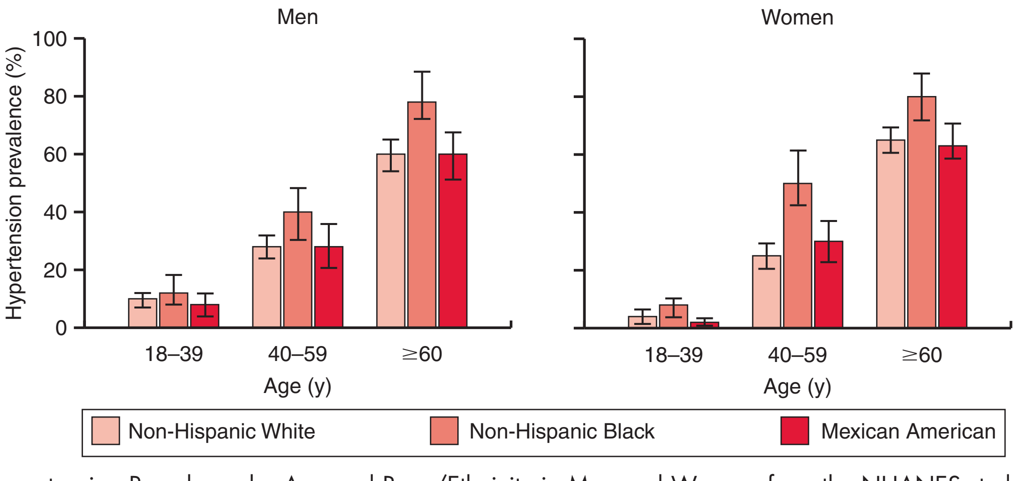

Figure 9–5 Hypertension Prevalence by Age and Race/Ethnicity in Men and Women, from the NHANES study. Error bars indicate 95% confidence intervals. Data are weighted to the U.S. population. (From Hajjar I, Kotchen TA: Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003;290:199-206.)

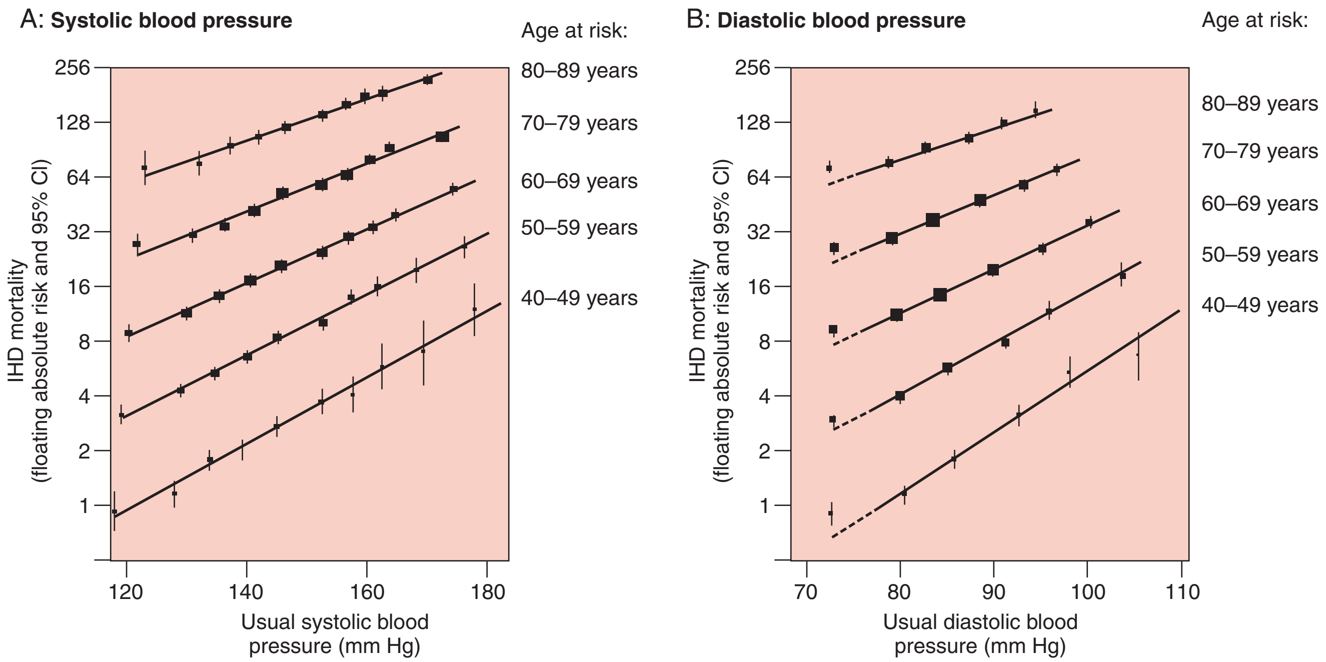

Figure 9–6 Coronary heart disease (CHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade. CHD mortality increases with blood pressure and with age. (From Prospective Studies Collaborative, Lancet 2002;360:1903.)

secondary prevention. For example, for persons with stage 1 hypertension (systolic blood pressure 140 to 159 mm Hg, diastolic blood pressure 90 to 99 mm Hg) and an additional CV risk factor, reduction in SBP of 12 mm Hg over a 10-year period can prevent 1 death for every 11 patients treated.[77] Moreover, clinical trials such as HOPE, EUROPA, and CAMELOT suggest that treatment to reduce blood pressure beyond recommended goals is beneficial in high-risk patients.[78-80]

Hypertension Treatment Recommendations

JNC VII provides guidelines for antihypertensive therapy for adults older than 18 years of age based on blood pressure levels measured as the mean of two or more blood pressure readings on two or more office visits.[62] The prehypertension designation recognizes that the blood pressure–cardiovascular risk relationship extends down to 115/75 mm Hg and that patients with prehypertension are at increased risk for developing hypertension.[70] Unlike JNC VI and the European Society of Hypertension-European Society of Cardiology guidelines, JNC VII does not stratify hypertensive individuals and antihypertensive management by cardiovascular risk factors (Table 9–5). The European guidelines delineate three stages of hypertension plus optimal, normal, and high-normal blood pressure in addition to classifying individuals as low, moderate, high, and very high risk according to their 10-year risk of cardiovascular disease.[81] The European guidelines have less aggressive treatment recommendations than JNC VII. Figure 9–7 shows the treatment algorithm for hypertension based on JNC VII.

Nonpharmacologic Treatment of Hypertension

Nonpharmacologic lifestyle modification is recommended for all patients with prehypertension (120 to 139/80 to 89 mm Hg). Nonpharmacologic strategies include weight loss, dietary changes and salt restriction, exercise, and avoidance of alcohol. Weight loss is effective for blood pressure reduction in both obese and nonobese individuals.[82,83] JNC VII recommends daily consumption of sodium chloride of 6 grams per day or less in normotensive individuals and sodium consumption of 2.4 grams per day or less in hypertensive individuals. Additionally, 30 minutes of moderate intensity exercise three times per week will reduce systolic blood pressure by 5 to 9 mm Hg in both normotensive and hypertensive individuals.[84] Finally, both acute and chronic alcohol use has been shown to increase blood pressure.[85]

Trial Data for Pharmacologic Treatment of Hypertension

Pharmacologic treatment is recommended for persons with a BP greater than or equal to 140/90 mm Hg, except in persons with diabetes or chronic kidney disease wherein treatment should be instituted for BP greater than or equal to 130/80 mm Hg. Although it is cost effective to treat low-risk patients with mild hypertension (140 to 150/90 to 99 mm Hg), JNC VII does not endorse treatment of lower blood pressures because of insufficient clinical trial evidence to support such treatment.[76] Despite appropriate pharmacologic treatment of hypertensive individuals, NHANES and the Western Infirmary in Glasgow data showed that treated hypertensives have a higher mortality than nonhypertensive individuals;

Table 9–5 Classification and Management of Blood Pressure in Individuals Older Than 18 Years

BP Classification	Systolic BP, mm Hg*		Diastolic BP, mm Hg*	Management* Lifestyle Modification	Initial Drug Therapy: Without Compelling Indication	Initial Drug Therapy: With Compelling Indication
Normal	<120	and	<80	Encourage		
Prehypertension	120-139	or	80-89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications†
Stage 1 hypertension	140-159	or	90-99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or	≥100	Yes	Two-drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)‡	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium channel blocker.
*Treatment determined by highest BP category.
†Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mm Hg.
‡Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.
From Chobanian AV, Bakris GL, Black HR, et al: the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC 7 Report, JAMA 2003; 289:2560-71

women have a 30% increased risk, and men have a 36% increased risk of mortality over 9 years.[86]

Clinical trials have shown that blood pressure lowering with multiple drug classes (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, thiazide-type diuretics) all reduce the complications of hypertension.[75,80,87-89]

Pharmacologic Treatment of Hypertension

Table 9–6 shows various high-risk conditions associated with hypertension and the recommended drug therapies. ALLHAT and JNC VII recommend thiazide-type diuretics as first-line therapy for blood pressure reduction, given the long clinical experience, clinical trial data, and the cost effectiveness of this regimen.[87] When used in combination with other antihypertensives, diuretics also enhance the efficacy of other antihypertensive agents. Selection of alternative or additional antihypertensive agents should be driven by compelling comorbid conditions and by the severity of hypertension. If initial blood pressure is greater than 20/10 mm Hg above goal, JNC VII recommends initiating two agents. In the ALLHAT trial, less than 30% of participants achieved goal blood pressure of less than 140/90 mm Hg on monotherapy.[87] When initiating multiple BP-lowering agents in patients with orthostatic hypotension, diabetes, autonomic dysfunction, and advanced age, an enhanced schedule of monitoring of the patient is suggested to detect adverse reactions early. β-Blockers are recommended as first-line therapy in CHD. Hypertensive patients with stable angina can be treated with β-blockers or calcium channel blockers.[62] In the context of an acute coronary syndrome, both β-blockers and ACE inhibitors are recommended.[90] In post-MI hypertensive individuals, β-blockers, ACE inhibitors, and aldosterone antagonists are recommended.[62] Hypertension precedes the development of heart failure in 90% of patients and hypertension increases the risk of heart failure twofold in men and threefold in women. Patients with asymptomatic LV dysfunction should be treated with an ACE inhibitor and β-blocker therapy.[91-93] Patients with symptomatic LV dysfunction should also be treated with angiotensin-receptor blockers, aldosterone antagonists, and loop diuretics.[94]

Diabetics with hypertension have a reduced life-expectancy versus nondiabetics with hypertension. In the UKPDS trial, diabetics whose blood pressures were tightly controlled had decreased risks of death, diabetic complications, stroke, and microvascular disease compared with their counterparts who had less tight BP control.[95] Additionally, the Hypertension Optimal Treatment (HOT) study revealed a 50% reduction in cardiovascular events among diabetics with tightly controlled blood pressure (mean DBP 81 mm Hg) compared with those diabetics with less tightly controlled blood pressure (mean DBP 85 mm Hg).[96] Both UKPDS and HOT imply that blood pressure goals should be lower in diabetics and that small differences in blood pressure equate to large differences in clinical outcomes. Therefore, JNC VII recommends that the goal BP in diabetics be less than 130/80 mm Hg. Most patients require two agents to achieve this goal.

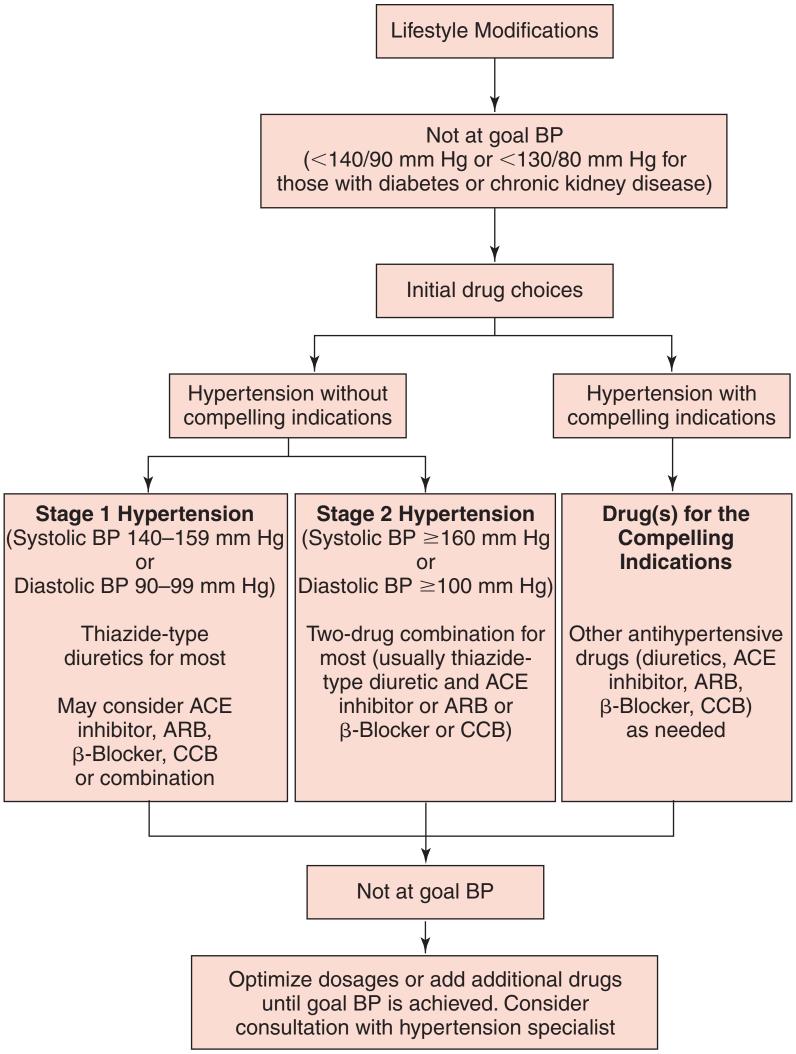

Figure 9–7 Algorithm for the treatment of hypertension: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium channel blocker. (From Chobanian AV, Bakris GL, Black HR, et al: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 2003;289:2560-71.)

Patients with chronic kidney disease represent another group of patients in whom tight blood pressure control is warranted. Chronic kidney disease is defined as an estimated GFR of less than or equal to 60 mL/min per 1.73 m^2 or a creatinine >1.5 mg/dL in men or >1.3 mg/dL in women. A meta-analysis of randomized controlled trials of patients with nondiabetic kidney disease found that the lowest risk of progression of kidney disease and of CHD was at SBP between 110 to 129 mm Hg.[96] In patients with chronic kidney disease, the goal BP should be less than 130/80 mm Hg. ACE inhibitors and angiotensin receptor blockers have been shown to retard the progression of nondiabetic kidney disease.[97]

Left ventricular hypertrophy (LVH) is an independent risk factor for the development of cardiovascular disease and confers a twofold increased risk of cardiovascular death in men and women.[98] LVH is associated with hypertension, obesity, excess dietary salt, and family history of LVH.[99] Regression of LVH is associated with aggressive blood pressure control due to lifestyle modification and all antihypertensive drug classes, except direct vasodilators.[100,101] Regression of LVH is also associated with cardiovascular risk reduction.[102,103]

Despite the availability of effective antihypertensive therapies, and the clear graded relationship between hypertension and cardiovascular risk, only 30% of hypertensive individuals are aware of their diagnosis and less than one half of these individuals receive adequate treatment.[104] According to JNC VI, rates of blood pressure control are lowest among Mexican-Americans and Native Americans.[105] Black Americans have a higher prevalence of hypertension and its complications than do other race/ethnic groups—a finding that may be related to biologic as well as socio-environmental influences. Studies have shown improved blood pressure lowering with calcium channel blockers and diuretics as opposed to β-blockers and ACE inhibitors in the black population.[87] Although two thirds of the elderly population have hypertension, blood pressure control among the elderly is the lowest among hypertensives owing to underdiagnosis, the presence of comorbidities, and adverse side effects from medications.[104]

SMOKING

According to the CDC National Health Interview Survey, the prevalence of cigarette smoking among U.S. adults is 21.6%.[106] Smoking rates progressively increase with decreasing socio-economic status. The ARIC study demonstrated that tobacco

Table 9–6 Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

High-Risk Conditions with Compelling Indication*	Recommended Drugs						Clinical Trial Basis†
	Diuretic	β-Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist	
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES
Post-myocardial infarction		•	•			•	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESU
High coronary disease risk	•	•	•		•		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE
Diabetes	•	•	•	•	•		NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease			•	•			NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	•		•				PROGRESS[35]

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; AIRE, Acute Infarction Ramipril Efficacy, ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin-receptor blocker; BHAT, β–Blocker Heart Attack Trial; CCB, calcium channel blocker; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; MERIT-HF, Metroprolol CR/XL, Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation-American Diabetes Association; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist, Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; Valsartan Heart Failure Trial.

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.

†Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.

From Chobanian AV, Bakris GL, Black HR, et al: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Preassure: The JNC 7 Report JAMA 2003; 289:2560-2571.

caused a 50% increase in the progression of atherosclerosis based on measurements of carotid intimal-medial thickness.[107] Epidemiological studies have reported a 20% to 30% increased risk of CHD among smokers. Furthermore, angiographic studies confirm that tobacco use is associated with more rapid progression of atherosclerotic lesions and the development of new lesions.[108] For individuals who smoke one pack of cigarettes per day, the RR of MI is sixfold higher for men and threefold higher for women compared with nonsmokers.[109] Meanwhile, the INTERHEART study reported that smoking accounted for 36% of population attributable risk of a first myocardial infarction.[57] In addition, passive cigarette exposure confers a 20% increased risk of CHD and death to nonsmokers, such that it is estimated that 40,000 annual CHD deaths in the United States are caused by secondhand smoke.[110,111] There is a dose-response relationship between passive cigarette exposure and CHD.[112]

Among individuals without CHD, smoking cessation reduces CHD event rate by 7% to 47%.[113,114] The RR of CHD in smokers is reduced within 1 year of quitting. After 5 years of smoking cessation, the CHD risk of former smokers approaches that of nonsmokers.[115] However, the risk for lung, pancreatic, and stomach cancers, as well as for chronic obstructive pulmonary disease, persists for over 10 years. Individuals who continue to smoke in the presence of known CHD have an increased risk of recurrent infarction and death.[116] With the cessation of tobacco use, the risk of recurrent myocardial infarction is reduced by 50%. Post-CABG patients who continue to smoke have a 75% and a 41% increased risk of CHD death and need for revascularization, respectively, compared with those who quit.[117] Similarly, post-angioplasty patients who continue to smoke have a 49% and 44% increased risk of CHD mortality and total mortality, respectively, compared with post-angioplasty patients who quit.[118]

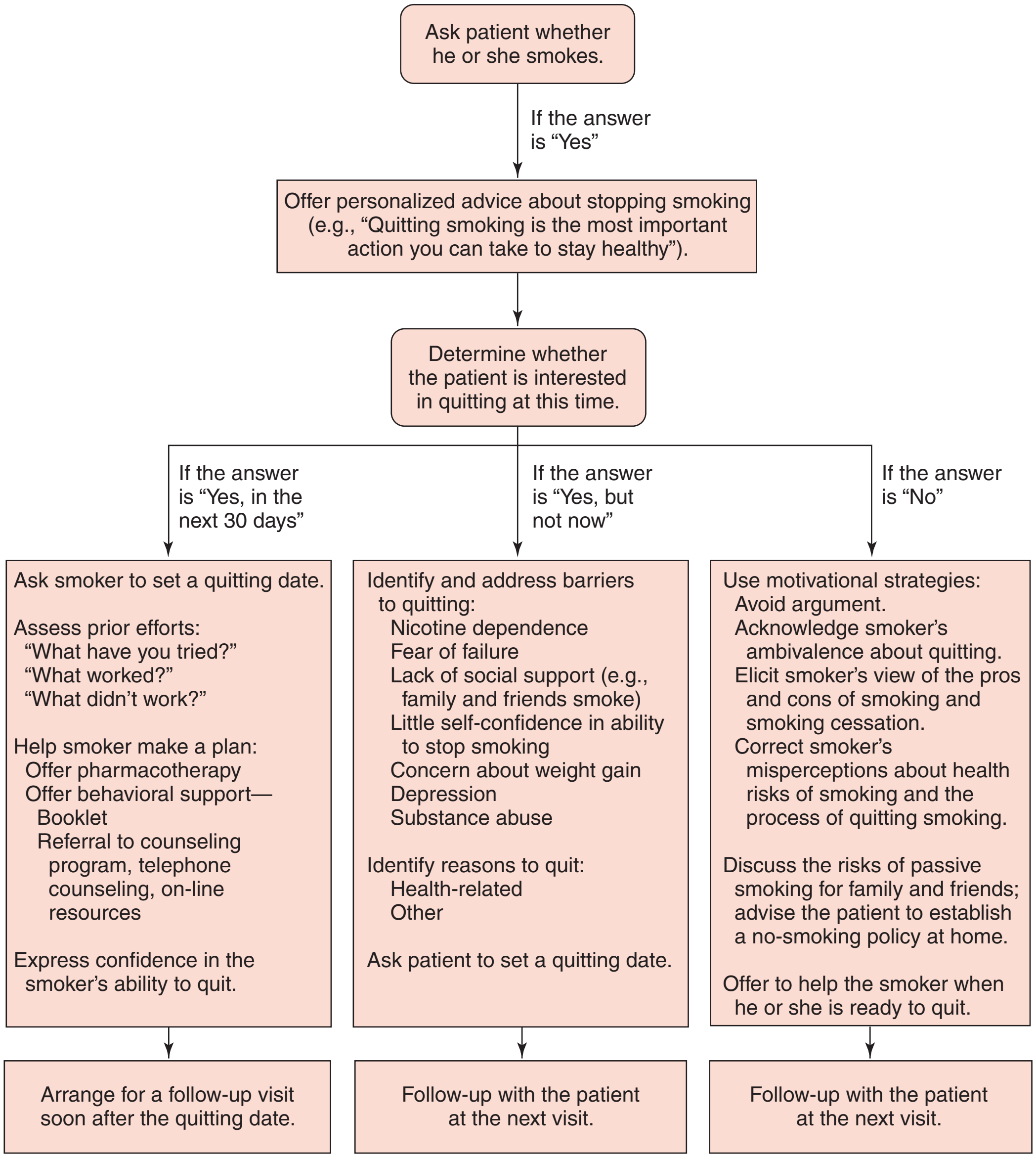

Figure 9–8 Smoking cessation strategy for physicians. This strategy uses the five steps recommended in Public Health Service guidelines: Ask, advise, assess, assist, and arrange follow-up. (From Rigotti N: Clinical practice: Treatment of tobacco use and dependence. N Engl J Med 2002;346[7]:506-12.)

Smoking Cessation Interventions

Reduction in cigarette use requires an improvement in awareness of the adverse cardiovascular outcomes associated with its use among smokers; 60% of two-pack per day smokers were unaware that their cigarette use increases their risk of CHD.[119] Physicians also need to improve communication with patients regarding cessation.[120,121] Figure 9–8 outlines a smoking cessation strategy for physicians. Table 9–7 illustrates drugs used for smoking cessation.

ATHEROGENIC DIET

Poor diet and a sedentary lifestyle are leading causes of preventable death, second only to tobacco use.[122] Diets high in cholesterol and rich in animal fats are linked to the development of CHD, whereas diets rich in vegetables, cereal grains, and fish are associated with prevention of CHD and stroke.[123,124] The Seven Countries Study identified the correlation between high fat/high cholesterol diets and CHD mortality.[124] It had been assumed that the harmful effect of the Western diet is mediated through saturated fat, cholesterol, and the effect of dietary sodium on the lipid profile, BMI, blood pressure, and insulin resistance. However, increasing evidence suggests that diet affects CHD risk beyond its effect on traditional cardiovascular risk factors.[125]

Dietary Fats

Dietary substitution of mono- and polyunsaturated fats for saturated fats improves lipid profiles and reduces CHD risk.[126-128] Trans fatty acids such as those found in stick margarine, vegetable shortening, and deep fat fried foods, increase

Table 9–7 Drugs Used for Smoking Cessation

Product	Daily Dose	Duration of Treatment	Common Side Effects	Advantages	Disadvantages
Nicotine-replacement therapy					
Transdermal patch* 24 hr (e.g., Nicoderm CQ) 16 hr (e.g., Nicotrol)	7-, 14-, 21-mg patch worn for 24 hr† 15-mg patch worn for 16 hr	8 wk 8 wk	Skin irritation, insomnia	Provides steady level of nicotine; easy to use; unobtrusive; available without prescription	User cannot adjust dose if craving occurs; nicotine released more slowly than in other products
Nicotine polacrilex gum (Nicorette)* 2 mg (<25 cigarettes/day) 4 mg (≥25 cigarettes/day	1 piece/hr (<24 pieces/day)	8-12 wk	Mouth irritation, sore jaw, dyspepsia, hiccups	User controls dose; oral substitute for cigarettes; available without prescription	Proper chewing technique needed to avoid side effects and achieve efficacy ‡; user cannot eat or drink while chewing the gum; can damage dental work; difficult for denture wearers to use
Vapor inhaler (Nicotrol Inhaler)*	6-16 cartridges/day (delivered dose, 4 mg/cartridge)	3-6 mo	Mouth and throat irritation, cough	User controls dose; hand-to-mouth substitute for cigarettes	Frequent puffing needed; device visible when used
Nasal spray (Nicotrol NS)*	1-2 doses/hr (1 mg total; 0.5 mg in each nostril) (maximum, 40 mg/day)	3-6 mo	Nasal irritation; sneezing, cough, teary eyes	User controls dose; offers most rapid delivery of nicotine and the highest nicotine levels of all nicotine-replacement products	Most irritating nicotine-replacement product to use§; device visible when used
Non-nicotine therapy					
Sustained-release bupropion (Zyban or Wellbutrin SR)*	150 mg/day for 3 days, then 150 mg twice a day¶	7-12 wk (up to 6 mo to maintain abstinence)	Insomnia, dry mouth, agitation	Easy to use (pill), no exposure to nicotine	Increases risk of seizure (≤0.1%)
Nortriptyline‖	75-100 mg/day**	12 wk	Dry mouth, sedation, dizziness	Easy to use (pill), no exposure to nicotine	Side effects common; should be used cautiously in patients with coronary heart disease
Clonidine‖	0.1-0.3 mg twice a day	3-10 wk	Dry mouth, sedation, dizziness	No exposure to nicotine	Side effects limit use

*This product has been approved by the U.S. Food and Drug Administration as a smoking-cessation aid. The Public Health Service clinical guidelines also recommend it as a first-line drug for smoking cessation.
†The starting dose is 21 mg per day unless the smoker weighs less than 45.5 kg (100 lb) or smokes fewer than 10 cigarettes per day, in which case the starting dose is 14 mg per day. The starting dose should be maintained for 4 weeks, after which the dose should be decreased every week until it is stopped.
‡The user should chew the gum slowly until he or she experiences a distinct taste, indicating that nicotine is being released. The user should then place the gum between the cheek and gum until the taste disappears to allow the nicotine to be absorbed through oral mucosa. The sequence should be repeated for 30 minutes before the gum is discarded. Acidic beverages (such as coffee and soft drinks) reduce the absorption of nicotine and should be avoided for 30 minutes before and during chewing.
§Tolerance develops to local side effects during the first week of use.
¶Treatment should be started 1 week before the quitting date.
‖This agent has not been approved by the U.S. Food and Drug Administration as a smoking-cessation aid. The Public Health Service clinical guidelines recommend it as a second-line drug for smoking cessation.
**Treatment should be started 10 to 28 days before the quitting date at a dose of 25 mg per day, and the dose should be increased as tolerated.
From Rigotti N: Clinical practice. Treatment of tobacco use and dependence. NEJM 2002;346:506-12.

LDL, total cholesterol, triglyceride, and Lp(a) levels, decreases insulin sensitivity, contributes to endothelial dysfunction, and increases platelet aggregation.[129] Dietary substitution of *cis* fatty acids for trans fatty acids reduces LDL and raises HDL.[130] Monounsaturated fatty acids, such as those found in olive oil, canola oil, and dairy products, decrease LDL oxidation and increase insulin sensitivity.[131] Similarly, polyunsaturated fats, such as those in safflower oil, sunflower oil, corn oil, and omega-3 fatty acids decrease total cholesterol, LDL cholesterol, inflammation and platelet aggregation, and they improve insulin sensitivity when substituted for saturated fats.[132] All three classes of fatty acids (saturated, monounsaturated, polyunsaturated fatty acids) increase HDL levels.

Primary prevention trials have shown that diets low in saturated fat and cholesterol reduce CHD risk. Early clinical trials demonstrated that long-term inpatients maintained on diets low in saturated fats and cholesterol had a 35% to 50% reduction in CHD endpoints.[133,134] Secondary prevention trials of dietary fats indicate that dietary intervention can reduce reinfarction rate and that the magnitude of benefit from dietary intervention trials is equivalent to that of lipid-lowering trials.[125,135] Notably, secondary prevention trials that studied diets low in total fat failed to show significant benefit in CHD outcomes. Thus, it appears that the type of fat, rather than total fat, is strongly associated with the prevention of recurrent CHD events. Observational angiographic studies also support the use of low fat diets.[136-139]

Omega-3 Fatty Acids

Evidence from multiple studies shows a positive relation between intake of omega-3 fatty acids and CVD risk reduction.[140,141] Fish and fish oil consumption lowers total cholesterol and LDL cholesterol, increases LDL particle size, improves endothelial function, and decreases inflammation and platelet aggregation.[142,143] A review of eleven studies of omega-3 fatty acids demonstrated an inverse relationship between omega-3 fatty acid intake and fatal CHD, a benefit that was most apparent among those at higher CHD risk.[140] Studies of secondary prevention of CHD with omega-3 fatty acids also demonstrate a protective effect of omega-3 fatty acids.[125,141,144] Omega-3 fatty acids have also been shown to prevent cardiac arrhythmias and to lower the risk of sudden death.[145]

Carbohydrates

Traditional dietary recommendations suggest high intake of complex carbohydrates and avoidance of simple sugars. Simple sugars have a high glycemic index, are more rapidly digested, and produce greater glycemic and insulinemic responses. A 10-year observational study of 75,521 women described a positive association between glycemic load and CHD that was strongest among obese women.[146]

Dietary trends have emphasized reduction in carbohydrate intake rather than dietary fat content. The Atkins diet (high protein, high fat, low carbohydrate diet) when compared with the AHA/NCEP low fat diet showed equivalent weight loss at 1 year, a decrease in triglyceride levels, and an increase in HDL cholesterol without a change in LDL cholesterol or total cholesterol levels.[147] In a review of 107 trials of low carbohydrate diets (Atkins, South Beach, Zone, Sugar Busters) weight loss was related to duration of diet adherence and not to carbohydrate intake. There was no significant adverse effect on blood pressure, lipid, glucose, or insulin levels; and CHD outcomes were not evaluated.[148]

Balanced Diet and Lifestyle Interventions

A balanced dietary approach rather than focused intervention on dietary cholesterol and fat has been studied in the secondary prevention of CHD. The combination of diet and lifestyle change results in a more powerful reduction in CHD endpoints than either intervention alone. A diet rich in fiber, omega-3 fatty acids and folate, low in trans fatty acids and glycemic load, and with a high ratio of polyunsaturated fats to saturated fats, coupled with moderate lifestyle changes including smoking cessation, low-moderate alcohol use, and daily exercise reduced CHD risk by 82% among women participating in the Nurses Health Study.[149] Similar outcomes on CHD risk resulting from diet plus lifestyle interventions were demonstrated in the Oslo Heart Study and the Lifestyle Heart study.[114] However, most primary prevention trials are limited by poor compliance and are inadequately powered to show CHD reduction.[150,151] **Therefore, current recommendations promote a well-balanced diet that is low in saturated fat, cholesterol, and sodium, rich in fruits and vegetables, and has less than 30% of its calories derived from fat. For patients with known CHD or dyslipidemia, less than 7% of calories should be from saturated fats and dietary cholesterol intake should be less than 200 mg per day. A diet rich in monounsaturated fats and omega-3 fatty acids is preferred.**

PHYSICAL ACTIVITY

Studies overwhelmingly demonstrate that in both high-risk patients and healthy individuals, exercise lowers CHD risk. In the Women's Health Initiative cohort, women who exercised vigorously or walked briskly for at least 2.5 hours per week had a 30% risk reduction in cardiovascular events.[152]

These findings were corroborated by the Nurses Health Study, the Harvard Alumni cohort study in men, and the Honolulu Heart Study in the elderly.[153,154] Moreover, large-scale studies indicate that vigorous exercise is not a requirement to observe CHD risk reduction. Cardiac rehabilitation and exercise are also effective in the secondary prevention of CHD.[155] Pooled data of 4000 post myocardial infarction patients show that cardiac rehabilitation reduces cardiovascular events and total mortality by 20% to 25%.[156,157] Additionally, angiographic data have demonstrated that exercise slows the progression of CAD.[158] Finally, an AHA consensus statement on exercise and physical activity recommends 30 minutes of moderate-intensity exercise on most, if not all days of the week, as do the CDC and the American College of Sports Medicine.[159,160]

OBESITY

Overweight is defined as a body mass index (BMI) of 25.0 to 29.9 and obesity as a BMI greater than or equal to 30.0 kg/m^2. Given the escalating worldwide prevalence of obesity, both the U.S. Surgeon General and the WHO have identified obesity as a major health problem.[161] Epidemiological studies

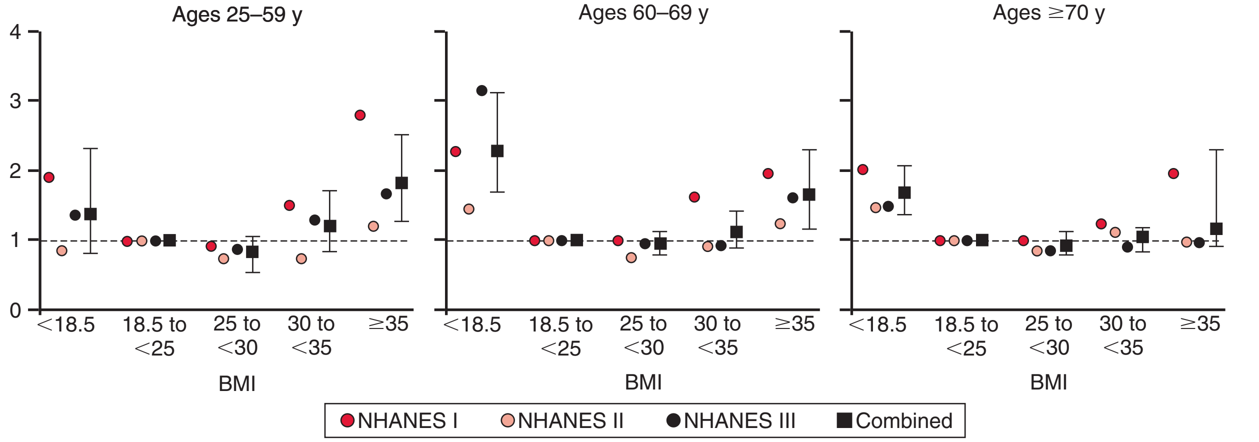

Figure 9–9 Relative risks of mortality by BMI category, survey, and age. U-shaped curve of mortality in which mortality increases with underweight, obesity, and morbid obesity. BMI, body mass index, measured as weight in kilograms divided by the square of height in meters. The reference category with relative risk 1.0 is BMI 18 to <25. Error bars indicate 95% confidence intervals. (From Flegal KM, Graubard BI, Williamson DF, Gail MH: Excess deaths associated with underweight, overweight and obesity. JAMA 2005;293:1861-67.)

demonstrate a positive association between overweight/obesity and all-cause mortality (Fig. 9–9).

The adverse consequences of obesity are mediated through other cardiac risk factors such as hypertension, left ventricular hypertrophy, insulin resistance, diabetes, dyslipidemia, inflammation, and the hypercoagulable state.[120] Although the American Heart Association identifies obesity as a cardiac risk factor, it is unclear whether obesity is itself an independent cardiac risk factor in multivariate analyses that account for hypertension, diabetes, and dyslipidemia.[120] Since the 1960s, there has been a greater decline in the prevalence of CHD risk factors such as dyslipidemia, hypertension, and tobacco use among overweight and obese populations compared with the lean population.[153] Since the U.S. trend for diabetes follows the increasing trend of obesity, the aforementioned net result of a decrease in CHD risk factors may be ameliorated.[162] Abdominal obesity measured by waist circumference confers greater cardiovascular risk than other forms of fat distribution.[62] The metabolic effects of abdominal fat likely contribute to the observation that obesity is a stronger predictor of CHD risk than physical inactivity, despite a common association between obesity and physical inactivity.[163]

Although weight loss improves dyslipidemia, insulin sensitivity, hemoglobin A1c, inflammatory biomarkers, and hypertension, it is unknown whether weight loss reduces cardiovascular events.[62,164,165] Weight loss is best accomplished through a combination of dietary changes and increased physical activity. Figure 9–10 outlines assessment and treatment algorithms for overweight persons.

METABOLIC SYNDROME

The metabolic syndrome is a disorder of insulin resistance exacerbated by obesity, sedentary lifestyle, and genetic predisposition. The Adult Treatment Panel III (ATP III) defined the metabolic syndrome as the presence of three or more of the following:

Waist circumference greater than 40 inches (102 cm) in men and 36 inches (88 cm) in women, serum HDL cholesterol level <40 mg/dL (1.04 mmol/L) in men and 50 mg/dL (1.29 mmol/L) in women, serum triglyceride level of 150 mg/dL (1.69 mmol/L) or more, BP of 130/85 mm Hg or more, serum glucose level of 110 mg/dL (6.1 mmol/L) or more.[24] Using the ATP III guidelines for the metabolic syndrome, 25% or 47 million of U.S. adults have the metabolic syndrome.[166] Although the metabolic syndrome also includes hemostatic dysregulation and inflammation, the ATP III definition does not include elevated fasting insulin, C-reactive protein, fibrinogen, PAI-1, or small dense LDL.[167] The WHO defines metabolic syndrome as the presence of diabetes, impaired glucose intolerance, impaired fasting glucose or insulin resistance plus two of the following:

Blood pressure ≥160/90, serum triglycerides ≥150 mg/dL (1.695 mmol/L), and/or serum HDL cholesterol less than 35 mg/dL (0.9 mmol/L) in men or less than 39 mg/dL (1.0 mmol/L) in women, central obesity with a waist-to-hip ratio <0.90 in men or <0.85 in women, or BMI less than 30 kg/m^2, microalbuminuria with a urinary albumin excretion rate more than or equal to 20 mcg/min or an albumin-creatinine ratio greater than or equal to 20 mg/g.[168]

Although the definition of metabolic syndrome includes established risk factors for CHD, the metabolic syndrome is considered an independent cardiac risk factor for both CHD and diabetes beyond the risk(s) attributed by obesity, hypertension, and dyslipidemia.[120,169] The metabolic syndrome confers a two- to fourfold increased risk of CHD and diabetes.[170,171] In NHANES, the presence of the metabolic syndrome in the absence of diabetes mellitus is associated with a hazard ratio of 2.02 (95% CI 1.42 to 2.89) for CHD mortality and HR 1.40 (CI 95% 1.19 to 1.66) for all-cause mortality (Fig. 9–11).[172]

Intensive lifestyle modification involving weight reduction and exercise is the cornerstone of prevention of CHD in persons with the metabolic syndrome. Given that diabetic vascular complications can be reduced by 50% with intensive treatment of dyslipidemia, hypertension, and blood glucose, and that there is an increased risk of CHD death among individuals with the metabolic syndrome, justification exists for intensive treatment of cardiac risk factors in those persons

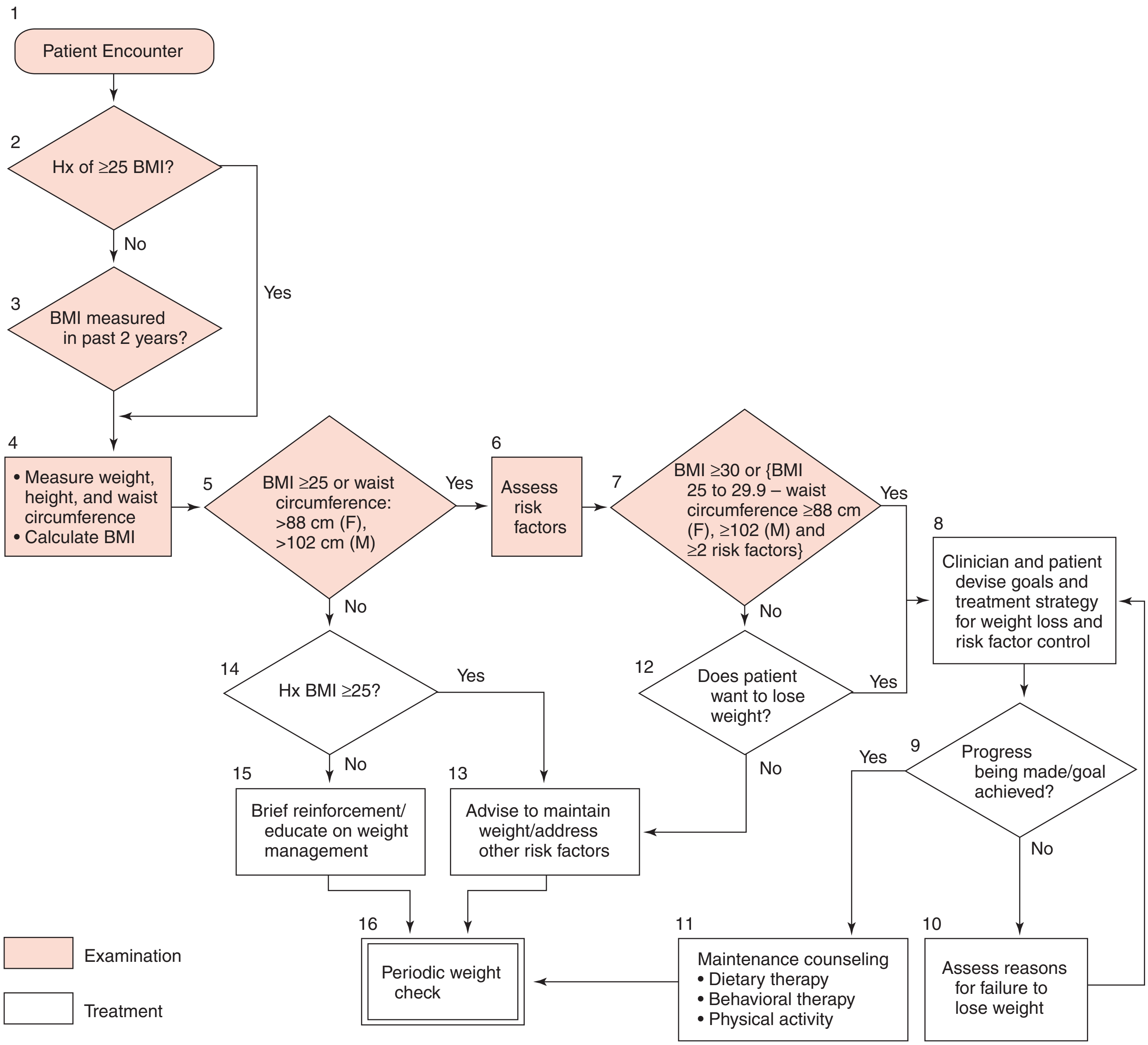

Figure 9–10 Assessment and treatment algorithm for overweight patients. BMI, body mass index; Hx, history. (From Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, Md, National Heart, Lung, and Blood Institute, 1998.)

with this diagnosis.[173] For high-risk individuals, pharmacologic therapy may be directed at metabolic risk factors—for example, metformin and thiazolidinediones improve insulin resistance and thus may play a role in preventing CHD. Thiazolidinediones may also exert anti-inflammatory effects in addition to their glucose-lowering effect.[174,175] Ongoing trials are evaluating the efficacy of thiazolidinediones for CHD in patients with impaired glucose tolerance as well as overt diabetes. ACE inhibitors may also be beneficial in the metabolic syndrome for both blood pressure reduction and amelioration of insulin resistance.[176] In the metabolic syndrome, NCEP guidelines should be used for recommendations on the management of dyslipidemias. Low-dose aspirin should be considered on an individual basis in metabolic syndrome patients for the primary prevention of CHD.

DIABETES

Diabetes mellitus is extremely common in the United States and the prevalence is expected to increase.[177] The prevalence of diabetes is highest among African and Native Americans and increases with age. Diabetes is associated with a two- to fourfold increased risk of CHD and stroke, independent of other cardiac risk factors.[9,178-180] The American Heart Association and NCEP/ATP III assigns equivalent risk for

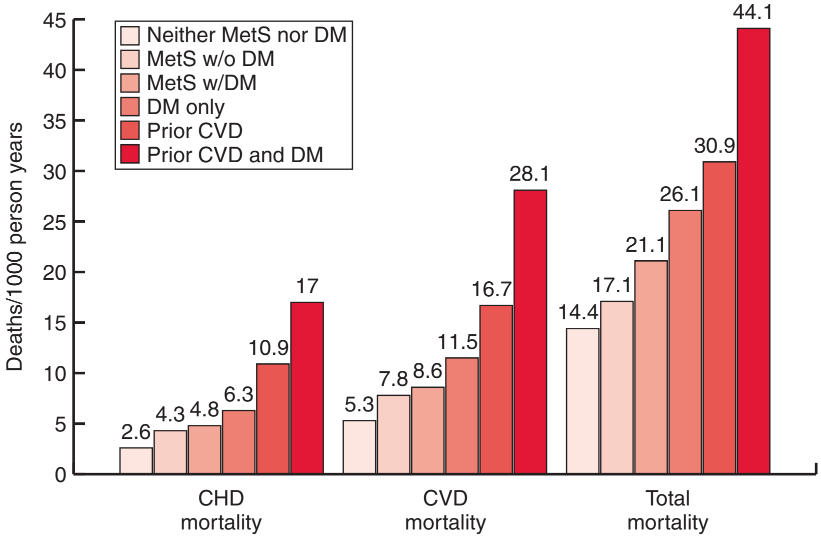

Figure 9–11 Age and gender-adjusted CHD, CVD, and total mortality in U.S. adults with metabolic syndrome (MetS) with and without diabetes mellitus (DM) in the NHANES II study of 6244 adults followed for 13.3 years. (From Malik S, Wong ND, Franklin SS, et al: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110:1245-50.)

CHD events to diabetics without a history of CHD and nondiabetic patients with CHD.[24,120,181]

The association between glucose intolerance/insulin resistance and cardiovascular risk is not limited to diabetics.[182] There is also a graded rise in cardiovascular risk below the diagnostic threshold for overt diabetes. Diabetes promotes CHD through dyslipidemia, thrombogenicity, endothelial dysfunction, inflammation, and hyperinsulinemia. Twenty-five percent of type II diabetics have dyslipidemia, and 80% of type II diabetics have hypertension.[183,184]

Although strict glycemic control prevents the microvascular complications of diabetes mellitus, the impact of strict glycemic control on macrovascular complications remains unclear.[174,185] The Diabetes Control and Complications Trial (DCCT) of type I diabetics showed that patients randomized to tight glycemic control had less progression of carotid intima-medial thickness over 6 years of follow-up compared with conventional glycemic control and decreased cardiovascular events over 17 years of follow-up.[186,187] However, in the United Kingdom Prospective Diabetes Study where diabetics were randomized to intensive versus conventional glycemic control, there was no significant difference between the two groups in myocardial infarction and stroke with each point of A1c reduction. However, the observation was that the A1c goal in the intensive arm was above that recommended by current guidelines.[188]

Cardiovascular Risk Reduction in Diabetes

The benefit of cardiac risk factor reduction is well documented in diabetes mellitus. Smoking cessation, weight loss, aggressive blood pressure and serum lipid control, as well as the use of low-dose aspirin, confer a mortality benefit in diabetics.[189] Tight blood pressure control might provide greater population cardiovascular risk reduction than intensive glycemic control (Table 9–8); efficacy has been demonstrated for calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers.[190]

The cardiovascular benefit of lipid-lowering in diabetics has been best studied using HMG-CoA reductase inhibitors. In the Heart Protection Study (HPS), 6000 patients were randomized to simvastatin or placebo; lipid lowering in patients with existing CHD resulted in a 27% risk reduction in major cardiovascular events.[69] The Collaborative Atorvastatin Diabetes Study (CARDS) trial evaluated atorvastatin for primary prevention of CHD in diabetics with normal LDL levels; atorvastatin was associated with a relative risk reduction of 36% to 37% in acute coronary syndrome and major cardiovascular events.[28] Fibrates have also been shown to reduce CHD mortality in secondary prevention.[50]

The cornerstone to CHD prevention in diabetics is lifestyle modification through weight loss. Although there remains a lack of consistent prospective evidence in support of tight glycemic control in the prevention of macrovascular disease, patients should attempt to normalize their A1c to prevent microvascular complications. According to the AHA, NCEP, and the American Diabetes Association, LDL should be aggressively reduced to less than 100 mg/dL for primary prevention of CHD in diabetic patients.[62,120] Similarly, the AHA recommends aggressive control of blood pressure to less than 130/80 mm Hg.[120]

According to the AHA/ACC, exercise treadmill testing in asymptomatic diabetic patients is a class 2b recommendation.[191] The American Diabetes Association/ACC Consensus Statement on Diabetes and Cardiovascular Disease in 1998 recommended noninvasive cardiac testing of asymptomatic diabetics who have peripheral arterial disease, cerebrovascular disease, ECG changes at rest, or two or more cardiac risk factors.[192]

ALCOHOL USE

Alcohol intake (one drink daily for women and two drinks daily for men) is associated with decreased CHD events and stroke in a relationship that is U or J shaped in nature with increasing alcohol consumption.[193-195] A meta-analysis of the risk of stroke and increasing alcohol intake demonstrated that there was a 28% decrease in ischemic stroke among those participants who consumed 12 to 24 g/d of alcohol.[196] However, the mechanism through which alcohol attenuates CHD risk remains uncertain, but is likely related to its effect on HDL-C

Table 9–8 The Effectiveness of Hypertension versus Glucose Control in the United Kingdom Prospective Diabetes Study

		Tight Blood Pressure Control†‡			Tight Glucose Control†		
Endpoint	Strategy	8.4-y Event Rate, n/n	10-y Absolute Risk Reduction	10-y NNT_B	10-y Event Rate, *n*/*n*	10-y Absolute Risk Reduction	10-y NNT_B
Any diabetes endpoint	Conventional Intensive	170/390 259/758	– 0.112 (0.05 to 0.17)§	– 8.9	438/1138 963/2729	– 0.032 (0.00 to 0.07)§	– 31.2
Diabetes-related death	Conventional Intensive	62/390 82/758	– 0.061 (0.02 to 0.11)§	– 16.4	129/1138 285/2729	– 0.009 (–0.01 to 0.03)	– 112.1
All-cause mortality	Conventional Intensive	83/390 134/758	– 0.043 (–0.01 to 0.10)	– 23.3	213/1138 489/2729	– 0.008 (–0.02 to 0.04)	– 125.3
Myocardial infarction	Conventional Intensive	69/390 107/758	– 0.043 (–0.01 to 0.09)	– 23.3	186/1138 387/2729	– 0.022 (0.00 to 0.05)	– 46.2
Stroke	Conventional Intensive	34/390 38/758	– 0.044 (0.01 to 0.08)§	– 22.7	55/1138 148/2729	– 0.006 (–0.02 to 0.01)	– 169.40‖
Peripheral vascular death or amputation	Conventional Intensive	8/390 8/758	– 0.012 (–0.01 to 0.03)	– 83.3	18/1138 29/2729	– 0.005 (0.00 to 0.01)	– 192.7
Microvascular	Conventional Intensive	54/390 68/758	– 0.058 (0.02 to 0.10)§	– 17.2	121/1138 225/2729	– 0.024 (0.00 to 0.05)§	– 41.9

* Values in parentheses are 95% CIs. NNT_B: number needed to treat for benefit.
† Achieved mean blood pressure was 154/87 mm Hg in the control group versus 144/82 mm Hg in the tight blood pressure control group; achieved mean hemoglobin A1c level was 7.9% in the control group versus 7.0% in the tight glucose control group.
‡ Mean follow-up in the blood pressure trial was 8.4 years; the crude event rate is presented for this 8.4-year follow-up, whereas the absolute risk reduction and the number needed to treat for benefit are standardized to a 10-year time frame to allow a more direct comparison with intensive blood glucose control.
§ Statistically significant relative risk reduction in primary data.
‖ For stroke, intensive glucose control led to a trend toward harm rather than benefit. As a result, the presented statistic is the number needed to harm.
From Vijan S, Hayward RA: Treatment of hypertension in type 2 diabetes mellitus: Blood pressure goals, choice of agents, and setting priorities in diabetes care. Ann Intern Med 2003;138:593-602

and other lipoprotein levels,[197] as well as its effect on inflammation.[198,199] Data suggest that 50% of the protective effect of alcohol is mediated through an increase in HDL-C concentrations.[200] Emerging evidence also indicates that moderate alcohol consumers also have lower levels of CRP, tumor necrosis factor receptors, and interleukin-6.[198,199,201] Alcohol also has a complex relationship with hemostatic parameters; light to moderate alcohol intake is associated with decreased levels of fibrinogen, von Willebrand factor and factor VII, as well as lower levels of fibrinolysis among consumers of >7 drinks weekly.[202] Despite the preceding evidence, public health recommendations for alcohol use and CHD remain cautious owing to the detrimental societal, physiological (e.g., elevated blood pressure, cirrhosis, and cardiomyopathy), and psychological effects related to its consumption.

NOVEL RISK FACTORS OF CARDIOVASCULAR DISEASE

Although the treatment of hyperlipidemia and hypertension has resulted in substantial reductions in mortality from CHD, approximately 40% of persons who develop the disease have one or no traditional risk factors for IHD.[10] A large body of evidence suggests that inflammation plays a prominent role in the development of atherosclerosis.[12,203] Besides basic science data that confirm the role of endothelial dysfunction, oxidation of LDL-C, and hemostatic and thrombotic factors in CAD pathogenesis, angiographic and pathology data also demonstrate that MI occurs more often in coronary arteries that have <70% stenoses and that the aortas of children as young as 15 years of age have atherosclerotic precursor lesions as well.[204] Therefore, data have emerged regarding the role of inflammatory, thrombotic, and hemostatic markers such as high sensitivity C-reactive protein (CRP), fibrinogen, soluble intercellular adhesion molecule, interleukins, Lp(a) and homocysteine, and risk of CVD. Table 9–9 shows established and emerging biomarkers of CVD risk.[205] It is important to understand that for a biomarker to be of use in a clinical setting, it should fulfill several criteria including (1) evidence from multiple prospective studies that clearly establishes a relation between the biomarker and future risk of cardiovascular events; (2) the biomarker should provide independent risk information beyond that available from traditional CVD risk factors or risk scores such as the Framingham Cardiovascular risk score; and (3) standardized assays that are easy to use and are cost effective should be available.

Table 9–9 Clinical Epidemiology of Proposed Novel Biomarkers in the Prediction of Future Cardiovascular Events

Biomarker	Prospective Studies Convincing?	Standardized Commercial Assay Available?	Additive to Lipid Screening?	Additive to Framingham Risk Score?
Inflammation				
hsCRP	++++	+++	+++	++
sICAM-1	++	+/−	+	−
SAA	++	−	+	−
Interleukin-6	++	−	+	−
Interleukin-18	++	−	+	−
Myeloperoxidase	+	−	+/−	−
sCD40 ligand	+	−	−	−
Altered Thrombosis				
IPA/PAI-1	++	+/−	−	−
Fibrinogen	+++	+/−	++	−
Homocysteine	+++	+++	+/−	−
D-dimer	++	+	−	−
Oxidative Stress				
Oxidized LDL	+/−	−	−	−
Altered Lipids				
Lipoprotein (a)	+++	+/−	+/−	−
LDL particle size	++	+/−	+/−	−

hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor; SAA, serum amyloid A; t-PA, tissue-type plasminogen activator.
From Ridker PM, Brown NJ, Vaughan DE, et al: Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation 2004;109(25)IV6-19.

C-Reactive Protein

CRP has been the most extensively studied of the novel markers of CVD. Multiple prospective studies indicate that elevated CRP levels independently predict risk of MI, stroke, acute coronary syndrome and sudden death, and risk of recurrent CVD events.[206-208] Interestingly, CRP is specific for predicting CVD mortality and does not predict noncardiovascular mortality.[209] CRP is an acute-phase reactant that consists of five 23-kDa subunits and is produced by the liver in response to inflammatory stimuli and proinflammatory cytokines such as interleukin-6 (IL-6); CRP is also produced by coronary artery smooth muscle cells and affects adhesion molecule expression and activates complement.[210,211]

In studies of risk assessment, CRP has been demonstrated to add prognostic information at all levels of risk of the Framingham Cardiovascular Risk Score (Fig. 9–12).[212] Although CRP levels correlate with the total Framingham Cardiovascular Risk Score, they only minimally correlate with individual components of the score—suggesting that CRP might be capturing other aspects of CVD risk beyond those represented by the traditional CVD risk factors.[213] Additionally, other data show that CRP adds predictive information at all levels of LDL-C such that persons with elevated levels of CRP but low LDL-C levels have a higher absolute risk of cardiovascular events than those with high LDL-C and low CRP levels (Fig. 9–13).[212] CRP has been shown to add prognostic information at all levels of the metabolic syndrome.[214]

Although CRP levels can be lowered by behavioral and pharmacologic interventions, there are no prospective data that demonstrate that lowering CRP levels in apparently healthy persons will attenuate CVD risk. Physical activity, weight loss, smoking cessation, and lipid-lowering medications including statins lower CRP levels. For example, in a study of men participating in the Physicians Health Study, although aspirin treatment prevented the development of MI, the latter was related to baseline CRP levels/degree of inflammation. Aspirin reduced the risk of MI by 55.7% ($P = 0.02$) among men in the highest quartile compared with the lowest quartile of CRP where there was a 13.9% risk reduction in MI that did not reach statistical significance.[215] Most of the data on the association between CRP and lipid-lowering agents relates to the use of 3-hydroxy-3-methylglutaryl coenzyme/statin therapy. Data from a subgroup analysis of the Cholesterol and Recurrent Events (CARE) study showed that compared with placebo, pravastatin significantly reduced CRP levels and risk of recurrent MI at 5 years.[216] Other research in a primary prevention cohort from the Pravastatin Inflammation/CRP (PRINCE) study demonstrated a significant reduction in CRP levels after 6 months.[217] Importantly, the change in CRP levels noted with statin therapy is independent of change in LDL-C levels. Data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS-TexCAPS) among persons without a history of CVD demonstrated that lovastatin prevented coronary events in individuals with hyperlipidemia at all levels of CRP as well as in those with high CRP levels but total cholesterol to HDL-C ratios that were below median values (number needed to treat for 5 years to prevent 1 event = 47, $P = 0.005$ versus 43, $P = 0.02$).[59] The effect of statin therapy on CRP levels represents a class effect.

The AHA/CDC have issued clinical recommendations regarding the use of CRP for global risk assessment. They note that CRP levels <1 mg/L should be considered low risk, 1 to

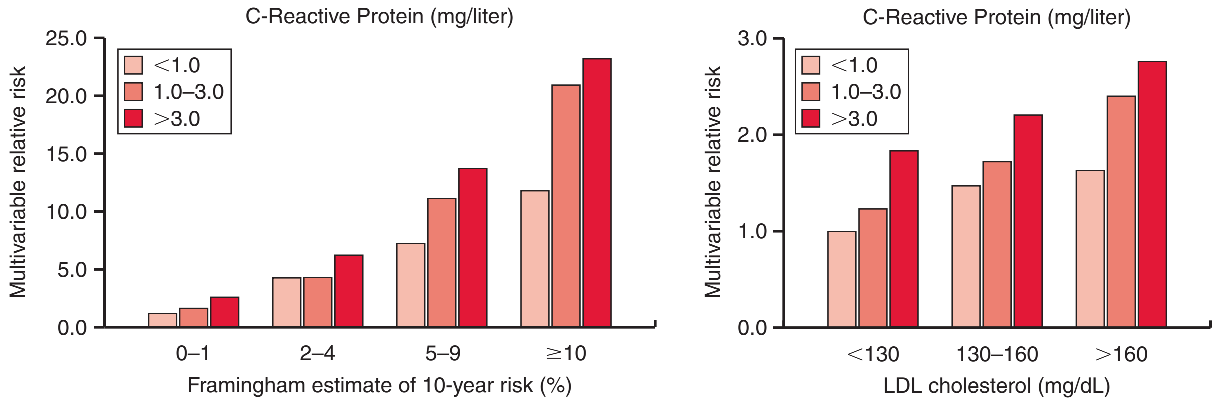

Figure 9–12 Multivariable adjusted relative risk of CVD according to all levels of LDL-C and the Framingham Cardiovascular risk score. To convert values for LDL-C to millimoles per liter (mmol/L), multiply by 0.02586. (From Ridker PM, Rifai N, Rose L, et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.)

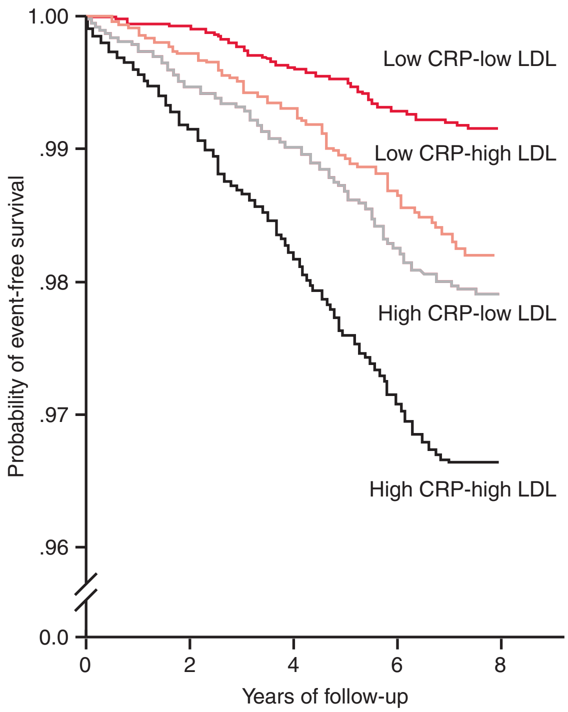

Figure 9–13 Event-free survival in apparently healthy women according to plasma levels of C-reactive protein and low density lipoprotein levels. (Ridker PM, Rifai N, Rose L, et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.)

3 mg/L as intermediate risk, and >3 mg/L as high risk for vascular disease. In addition to lipid screening, CRP screening should be performed at the discretion of the physician, particularly in those individuals who are at intermediate risk of vascular disease. It should be noted that CRP levels are affected by concurrent inflammatory illness, obesity, and hormone replacement therapy—all of which raise levels. Much of the data regarding CRP are limited to white populations, but emerging data that suggest that CRP levels might vary by race/ethnic group.[218,219] Primary prevention trials such as the Justification for the Use of statins in Primary Prevention: An Intervention Trial Evaluating Rousuvastatin (JUPITER) are in progress to evaluate whether lowering CRP levels among individuals without a history of CVD will result in a reduction of CVD events.[220]

Homocysteine

A meta-analysis of 30 trials of homocysteine, that included retrospective and prospective trials showed a 25% lower homocysteine level was associated with an OR 0.89 (95% CI 0.83 to 0.86) and 0.81 (95% CI 0.69 to 0.95) of CHD and stroke, respectively.[221] The association between homocysteine levels and CHD risk was independent, continuous, graded, and without a lower threshold beyond which the benefit is lost.

Low dietary intake of folic acid, vitamin B_6, and vitamin B_{12} are associated with hyperhomocysteinemia and increased risk of atherosclerosis.[222] A protective role of high dietary folic acid has been demonstrated among CHD-free men; a 55% reduction in the relative risk of CHD among Finnish men with high folic acid intake has been demonstrated.[223] Folic acid supplementation with 400 mcg daily lowers homocysteine levels by 30% to 42%.[224] It is unclear whether vitamin B_6 and B_{12} supplementation offer additional homocysteine lowering in the absence of nutritional deficiencies.[120]

Replacement of the noted vitamins can correct plasma levels of homocysteine and theoretically reduce the risk of future vascular events. Conflicting evidence exists regarding the use of folic acid supplementation in persons with established CHD. An open-label randomized trial of folic acid supplementation in stable CHD revealed no benefit at 2 years, whereas a randomized trial of supplementation with folic acid, vitamin B_6, and vitamin B_{12} in post-PTCA patients showed a decrease in adverse CHD events at 11 months in the treatment arm.[225,226] By contrast, a randomized trial of folic acid supplementation versus placebo after stent placement showed an increase in in-stent restenosis in the treatment arm.[227]

Although a large body of evidence shows that elevated homocysteine levels are associated with increased CHD risk, screening

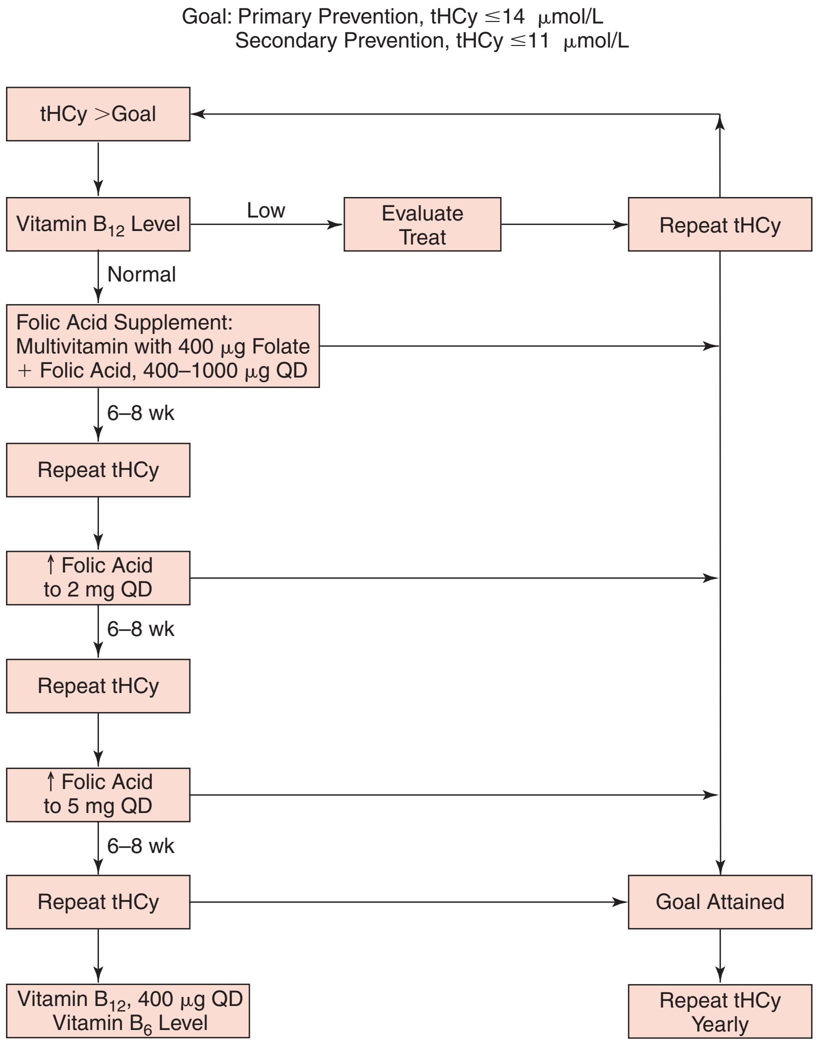

Figure 9–14 Suggested algorithm for treatment of hyperhomocysteinemia. (From Stein JH, McBride PE: Hyperhomocysteinemia and atherosclerotic vascular disease: Pathophysiology, screening, and treatment. Arch Intern Med 2002;158:1201-06.)

of the general population is not yet recommended.[120,228] At the population level in the United States, folic acid has been easily supplemented through the fortification of bread. The AHA recommends screening of persons who have a personal or family history of premature CHD in the absence of traditional risk factors, malnutrition, and malabsorption syndromes, hypothyroidism, chronic renal failure, systemic lupus erythematosus, unexplained venous thrombosis, and patients taking medications that increase homocysteine levels.[229] Screening should be deferred for 2 to 3 months after serious systemic illness. High-risk individuals without a history of CHD should be treated for primary prevention if their homocysteine levels exceed 14 µmol/L. Dietary supplementation with folic acid 1 mg/day is recommended (Fig. 9–14). The addition of vitamin B_6 10 mg/day and vitamin B_{12} 0.4mg/day has not been vigorously proven to be effective. If homocysteine levels fail to normalize in 6 weeks, the dose of folic acid may be increased. For adults with average CHD risk, a daily multivitamin that includes folate is suggested.

Lipoprotein (a)

Lipoprotein (a) has structural homology with plasminogen and is composed of LDL-C that has the apolipoprotein (a) 100 constituent linked by a disulfide bond. Because of its structural similarity to plasminogen, it might compete with the latter to inhibit fibrinolysis. Although its role in promoting CVD is unclear, it induces chemotaxis of monocytes, and affects PAI-1 and tissue factor expression.[51,230] Plasma concentrations of Lp(a) are dependent on APO A isoform size and are genetically influenced.[231]

Multiple studies indicate that elevated levels of Lp(a) predict vascular risk. Blacks tend to have higher Lp(a) levels than other race/ethnic groups but the importance of the latter as a risk factor in this population remains uncertain. Because there is minimal correlation between Lp(a) and traditional CVD risk factors, prospective data demonstrate that the adjustment for the latter results in nominal change in the overall combined risk ratio of 1.6 among persons in the highest tertile of Lp(a) compared with those in the lowest tertile.[232] At present, there are no data that indicate that Lp(a) adds predictive value to the Framingham risk algorithm. It is also unclear whether elevated Lp(a) levels predict CHD risk in all populations. As well, the standardization of commercial Lp(a) assays remains poor owing to varying sensitivity of the assays to APO A size making it difficult to use Lp(a) for widespread screening for CVD.[233] However, measurement of Lp(a) might be useful in persons with premature CHD, renal failure patients, and

among elderly men.[234,235] High-dose niacin reduces Lp(a) levels but the latter therapy has not been proven to reduce the risk of subsequent CHD events.

Hemostatic and Thrombotic Markers

Fibrinolysis and thrombosis are critical components in the pathogenesis of atherosclerosis. Impaired fibrinolysis is, in part, a result of an imbalance between clot dissolving elements such as t-PA and urokinase-type plasminogen activator and PAI-1. PAI-1 is ubiquitous in humans, has a relatively short half-life, and is produced by the vasculature, adipose tissue, and liver and is stored in large quantities in platelets.[236] Its production is regulated by inflammatory cytokines, neurohormonal and metabolic factors including glucose, glucocorticoid and glucosamine responsiveness. Plasma concentrations of PAI-1 are also affected by polymorphisms in the PAI-1 gene; the 4G/4G genotype is associated with the highest levels of PAI-1.[170] Basic science evidence demonstrates that transgenic mice that overexpress human PAI-1 develop coronary occlusions and MI [237] and that PAI-1 is localized in atherosclerotic plaques.[238-240] Several reports show that PAI-1 predicts IHD risk in healthy middle-aged men, young survivors of MI, and other post-MI patients.[241,242] However, there are no consistent prospective data that show that PAI-1 improves CVD risk prediction beyond that of traditional risk factors/algorithms. Moreover, the need for proper specimen collection, the circadian variation of PAI-1 activity (high levels in the morning and lower levels in the afternoon), and the responsiveness of PAI-1 expression to estrogen, insulin, and angiotensin II complicate the ability of PAI-1 usage in the clinical setting. Angiotensin converting enzyme inhibitors result in a decrease of PAI-1 antigen levels in humans.[243,244]

Tissue plasminogen activator is another member of the fibrinolytic system that is secreted by the vascular endothelium in response to bradykinin and substance P, is stored in endothelial cells, has a short half-life and unlike PAI-1 is not influenced by circadian factors.[205] Elevated levels of t-PA are associated with increased vascular risk[13,245]; t-PA is believed to interact with PAI-1 to form stable complexes that have a longer circulatory time than t-PA. The use of t-PA in clinical practice is also hindered by the lack of standardized commercial assays and prospective data that show that measurement of t-PA adds predictive utility to lipid screening or cardiovascular risk scores.

Fibrinogen

Multiple prospective studies have demonstrated a relationship between fibrinogen and future cardiovascular events. A meta-analysis of 22 studies found that the CVD risk estimate associated with the highest tertile of fibrinogen versus the lowest tertile was 1.99 (95% CI 1.85 to 2.13).[246] Elevated baseline levels of fibrinogen are also associated with an increased risk of stroke and peripheral arterial disease.[246,247] Factors that increase fibrinogen include smoking, diabetes, obesity, hormone replacement therapy, and age; levels are reduced by moderate alcohol use, exercise, and certain lipid-lowering agents—fibrates and niacin. Although fibrinogen predicts risk of vascular events, several challenges hinder its usefulness for risk assessment in the prevention of CVD, including the lack of clinical data that show benefit in reducing CVD events by lowering fibrinogen levels,[248] its strong correlation with levels of other inflammatory markers such as CRP (that might suggest that raised levels reflect the general inflammatory state of atherothrombosis) and sometimes wide variations in serum levels.

NONINVASIVE ASSESSMENT OF VASCULAR DISEASE

Appropriate assessment of asymptomatic patients at intermediate risk for vascular disease has been the subject of intense study over the past decade. Although low-risk persons do not need therapy, and high-risk persons usually qualify for defined interventions, intermediate-risk persons compose a group of people who need refined risk assessment. Imaging modalities might help to provide improved risk assessment among intermediate-risk persons.[249]

Ankle-Brachial Index

Screening for lower-extremity peripheral arterial disease (PAD) is performed using the ankle-brachial index (ABI), a ratio of systolic blood pressure in the ankle arteries to the systolic blood pressure in the brachial arteries. ABI is an inexpensive screening tool used for diagnosing peripheral arterial disease and increasing awareness of PAD in the primary care setting. Prevalence of peripheral arterial disease in primary care practices is high, and PAD is unlikely to be diagnosed. Because of the latter, PAD patients are less likely to be referred to smoking cessation programs or treated for their CVD risk factors.[250] In persons without peripheral arterial disease, systolic pressures are higher in the periphery than in vessels closer to the heart owing to arterial taper.[251]

Normal ABI values are generally >1.00 and ABI values <0.90 are sensitive and specific for the presence of peripheral artery disease.[252,253] Although there is good evidence that values <0.90 are abnormal, less is known about the meaning of borderline values. ABI categories include an ABI of 0.90 to 0.99 that represents borderline ABI; 1.10 to 1.29 is considered a normal ABI; and >1.30 a high ABI. The importance of this classification on clinical outcome is unclear.[254] A few studies have suggested that values >1.50 may represent calcification of peripheral arteries[255] but further study of such thresholds is needed.

Approximately 25% to 30% of elderly individuals have a low ABI. For example, among the elderly, a low ABI value carries a relative risk of 6.3 for a CVD mortality and 3.1 for all-cause mortality compared with normal ABI values.[256] The utility of ABI measurements has also been studied in different ethnic groups. The Multi-Ethnic Study of Atherosclerosis (MESA) found that ABI was significantly associated with the degree of subclinical atherosclerosis in the coronary and carotid arterial beds across ethnicities.[254]

Electron-Beam Computed Tomography

Because previous studies have indicated a relationship between coronary artery calcium and mural atheromatous plaque,[257-259] electron-beam, ultrafast CT (EBCT) was proposed as a way to measure and quantify coronary artery calcium levels.[260] Indeed, some studies have found a correlation

between the total mass of coronary artery calcium as reflected by the calcium score, and the total mass of atherosclerotic plaques as well as the number of arteries and segments with greater than 75% reduction in luminal diameter.[261-264] Coronary artery calcification and calcium score increases with age, and the usefulness of EBCT for identifying patients at higher risk for significant coronary artery disease decreases with increasing age.[260]

Some studies indicate that coronary calcium measurement can add incremental CHD risk prediction information for intermediate- to high-risk patients as well influence patient behavior.[265,266] For example, in one postmortem study, more than 97% of arterial segments without calcification were free of hemodynamically significant stenosis and hemodynamically significant stenosis was not present in vessels without calcification.[261] Also, some data show that self-referred subjects who have high coronary calcium scores were more likely to adhere to HMG-CoA reductase therapy than their counterparts with low scores.[267]

Potential limitations regarding the widespread use of EBCT include that its specificity is only 75% and that the total volume of calcification by EBCT may correlate more closely with the total burden of atherosclerotic plaque than with lumen stenosis.[267,268] Also, there may be limitations in the ability of the coronary calcium score to predict CHD risk in all ethnic groups. Additionally, the calcium screening method does not address the degree of plaque stability or give any physiologic information.

The AHA consensus statement on the use of electron-beam computed tomography for CHD screening [269] notes that, despite its high sensitivity, the low sensitivity of EBCT precluded, in part, recommendation for use to diagnose coronary artery disease.[270] Although EBCT might add information to traditional risk factors, EBCT cannot yet be used in lieu of coronary angiography.

Common Carotid Intima-Media Thickness (IMT)

Another measure of peripheral arterial disease is carotid intima-media thickness (IMT) by B-mode ultrasound.[271] IMT gives information on atherosclerotic wall changes that cannot be obtained by conventional contrast angiography or MRI.[272] Carotid arteries have been particularly favored for study as a peripheral artery because they are relatively superficial, large in caliber, and are relatively immobile, thereby allowing easy imaging.

The carotid IMT measure is associated with age, elevated levels of major cardiovascular risk factors such as dyslipidemia, hypertension, and cardiovascular disease.[273-277] Carotid IMT also correlates with the angiographic presence and extent of coronary artery disease.[278,279] For example, in populations without known coronary artery disease, high carotid IMT score is associated with an elevated risk for further cardiovascular events.[273,280] In one study, asymptomatic people older than the age of 50 years with abnormal intimal medial thickness (IMT) had a fivefold increased risk than that ascribed by traditional coronary risk factors for the occurrence of future cardiovascular events.[273,281,282] Another study demonstrated that carotid arterial intima-media thickness predicted coronary events in men 40 to 59 years of age who had previously had coronary artery bypass graft surgery.[281] Also, some evidence indicates that there may be incremental predictive value of carotid ultrasonography in assessing coronary risk in diabetic patients.[283]

Carotid IMT is affected by lifestyle factors such as cigarette smoking, cholesterol intake, and body mass index. Treatment of these factors results in improvement of IMT measurements; for instance, lipid lowering reduces cardiovascular events and mortality and decreases the degree of IMT.[284-286] Before routine measurement of IMT in clinical practice, methods of measurement must be standardized and precise thresholds must be set that accurately indicate levels of CHD risk.[287]

Exercise Testing

Exercise electrocardiography has been proposed as a screening tool for asymptomatic subjects thought to be at intermediate risk for developing clinical coronary disease. Important measures during exercise testing that predict CHD risk include nonelectrocardiographic measures such as exercise or functional capacity, chronotropic response, heart rate recovery, and the development of ventricular ectopy.[120] Many studies have shown that the most important marker of vascular risk yielded by exercise testing is the measure of functional capacity. Population-based studies have confirmed the importance of functional ability to predict CHD mortality and cardiovascular risk in asymptomatic patients.[288-290] The role of exercise testing in asymptomatic patients for primary prevention has not yet been clearly defined.[120] It is unknown whether routine exercise testing in selected asymptomatic patients attenuates cardiac morbidity and mortality.[291]

Psychosocial Factors

Some studies indicate a link between depression, anger, hostility, and IHD.[292,293] Most studies show an increase in risk of CHD events with higher depression scores. The data linking anxiety, anger, and hostility to IHD are not as consistent as the data related to depression and are limited among other issues by the lack of women in available research reports and nonstandardized screening instruments.[292,294] However, data from the Nurses Health Study showed that phobic anxiety as measured by the Crown Crisp index was associated with an increased risk of sudden cardiac death.[295] The mechanism linking psychological symptoms and IHD are complex and not well elucidated but include adverse lifestyle behaviors such as physical inactivity, noncompliance with care, smoking, hypercortisolemia, hemostatic perturbations, impaired vagal tone, and reduced heart rate variability.[292]

Low socioeconomic status is another factor associated with increased risk of CVD. Although socioeconomic status encompasses multiple factors including education, income, neighborhood environment, social status and support, the relationship between socioeconomic level and CVD is likely, in part, a result of chronic physical and psychological stress. Pathophysiologically, hypothalamic-pituitary axis dysfunction, lipid and hemostatic abnormalities all contribute to the physiological effects of chronic stress on the vascular system.[296,297] Interventions aimed at reducing morbidity and mortality related to psychological complaints should be multidisciplinary in nature and must encompass adequate screening and referral and management of affected patients. Table 9–10[294] outlines potential behavioral and medical interventions.

Table 9–10 Behavioral and Medical Interventions for Psychosocial Risk Factors

		Intensity of Intervention	
Type of Intervention	Targeted Condition	Less Intense*	More Intense
Exercise training	Psychologic distress	Exercise prescription plus general guideline	Supervised exercise
Nutritional counseling	Management of stress by overeating	Provide nutritional advice	Supervised dietary instruction, weight management, and behavior modification
Relaxation training	General stress and stress caused by specific situations	Advise patient to initiate relaxation training; provide audiotapes, videotapes, or instructional scripts	Teach muscle relaxation, imagery, autogenic training, diaphragmatic breathing, or biofeedback
Stress management	General stress and stress caused by specific situations	Recommend vacations, hobbies, yoga, relaxing music, pets, or pleasurable activities	Teach behavioral strategies (e.g., problem-solving, self-monitoring, appropriate goal-setting, relapse-prevention techniques)
Social support	Poor structural or functional support	Provide specific social suggestions (e.g., join walking groups or engage in socially altruistic activities)	Use staff as a support base, enroll patient in support group, or facilitate family involvement
Health information	Specific stress situations (e.g., at work or home) or low health literacy	Provide situation-specific information in the forms of books, articles, pamphlets, audiotapes, videotapes, or Web sites	Discuss and answer patient questions regarding materials related to health and treatment recommendations.

*Most amenable to direct cardiologist management.
From Rozanski A, Blumenthal JA, Davidson KW, et al: The Epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice. J Am Coll Cardiol 2005; 45:637-51

Postmenopausal State

Earlier observational studies such as the Nurses Health Study had suggested that users of estrogen had about one half the risk of CHD as nonusers (relative risk of 0.51, 95% CI of 0.37 to 0.70),[298] and that overall hormone replacement therapy (HRT) lowered CVD risk 40% to 50%. Given the other benefits of estrogen replacement, such as reduction in bone loss, it became common clinical preventive practice in the early 1990s to recommend hormone therapy for postmenopausal women, those women with coronary heart disease, and those at high risk for coronary heart disease.[299] However, a series of studies has emerged that disproves the original observations. Trials that used estrogen and medroxyprogesterone acetate among women with established angiographically verified coronary artery disease[300] and older women with coronary-artery atherosclerosis[301] showed that combination HRT treatment did not affect the progression of coronary atherosclerosis. Subsequently, the publication of the Heart and Estrogen/progestin Replacement Study (I and II) in secondary prevention, and the Women's Health Initiative Study (WHI) in primary prevention, changed the guidelines for hormone replacement therapy.

HRT and CHD Prevention

The HERS trial randomized 2763 women with known coronary artery disease to either estrogen plus medroxyprogesterone acetate or placebo and followed them for the occurrence of nonfatal myocardial infarction or CHD death for an average follow up of 4.1 years.[302] HRT treatment did not reduce the overall rate of CHD events and increased the rate of thromboembolic events (HR 2.89, 95% CI, 1.50 to 5.58). Higher CHD risk was observed during the first year of therapy, and although CHD risk decreased during years 3 to 5, this did not persist at long-term follow-up.[303]

The results of the Women's Health Initiative (WHI) echoed those of the HERS trial in a primary prevention population. Among 16,608 postmenopausal women without history of CHD, aged 50 to 79 years at baseline randomized to estrogen plus medroxyprogesterone acetate or placebo,[304] the overall risks of HRT exceeded the benefits after 5.2 years of follow-up. HRT was associated with a hazard ratio for CHD of 1.24 (95% CI, 1.00 to 1.54) compared with placebo.

Recommendations

In light of these findings, the U.S. Preventive Services Task Force (USPSF) issued recommendations for the prevention of chronic conditions in postmenopausal women in 2005.[305] Although the use of combined estrogen and progestin resulted in both benefits and harms—with benefits that include reduced risk for fracture and colorectal cancer—given recent data, they recommended against the routine use of combined estrogen and progestin or unopposed estrogen for the prevention of chronic conditions in postmenopausal women (Grade D recommendation). Similarly, the 2004 AHA Scientific Statement for Cardiovascular Disease Prevention in Women[306] concluded that combined estrogen plus progestin hormone therapy should not be initiated to prevent CVD in postmenopausal women

(Class III, Level A) and that combined estrogen plus progestin hormone therapy should not be continued to prevent CVD in postmenopausal women (Class III, Level C).

CAD IN DEVELOPING COUNTRIES

While CVD rates have been declining in many developed nations, in developing nations CVD rates continue to increase and account for 80% of worldwide CVD burden. It is estimated that there were 17 million CVD deaths worldwide in 2002—representing the main cause of death.[1] In developing nations, the mortality from CAD is estimated to be greater than 4.5 million, a number that is expected to exceed 8 million by 2020. Some clinicians estimate a 120% and 137% increase in CAD death rates among women and men, respectively.[306,307] Prevalence rates for CAD will be fueled by explosions in the number of persons affected by diabetes, obesity, and the continued increase in tobacco use—particularly among the youth. Chronic diseases, of which CVD represents the majority of cases, prevails over infectious diseases and has resulted in the so called "double burden of disease" in developing nations where early in life, persons/populations are afflicted with infectious diseases only to later be plagued with chronic illnesses such as CAD due to an increase in life expectancy in many countries.

The continuing increase of CAD cases in developing countries can be attributed to multiple factors including, but not limited to, societal transitions from rural to urban communities, the adoption of Western diets that are high in saturated fats and sugars, and improvements in longevity.[308] Although there is a paucity of data from most developing countries, CAD accounted for at least one third of CVD deaths in India and more than fifty percent of deaths in urban areas of China.[308,309] Among black Africans, CAD prevalence is relatively low compared with urban whites and Asians; however, statistics are hampered by the lack of comprehensive epidemiological studies and disease misclassification. The INTERHEART study, a case control study of modifiable risk factors for MI in 52 countries demonstrated that psychosocial factors, smoking, and APO B/APO A1 ratio were dominant factors in the risk for MI worldwide, and that the traditional risk factors for MI in market economies accounted for approximately 90% of the population attributable risk for MI. In the outpatient setting, the Reduction of Atherothrombosis for Continued Health (REACH) Registry collected data on atherosclerosis risk factors in 44 countries demonstrated that risk factor profiles for CAD are similar across non-African nations across the world.[310] These data suggest that the basic tenets of prevention of CAD in developing nations could be similar to those that govern prevention goals in industrialized nations.[57]

The operative aspect of prevention strategies in developing countries remains a challenge. First, the "double burden of disease" places an enormous strain on government and international agency budgets. Additionally, many economies benefit significantly from the production of harmful tobacco products, thereby ensuring that prevention efforts in some nations will conflict with national economies—making it harder to implement beneficial strategies. Public health programs to promote healthy dietary and physical activity strategies are in direct competition with individual and societal wealth transitions that confer more urban living and Western diets. Effective prevention strategies in developing nations should include the collection of risk factor information and determinants of behavior in an organized manner through large-scale epidemiological studies, public programs that promote healthy eating and physical activity, accurate education/communication of current CVD disease burden to key policy makers, provision of inexpensive effective pharmacologic therapies, and the control of tobacco products (Table 9–11).[311]

Table 9–11 Proposed Strategies to Deal with CVD in Developing Countries

1. Development of reliable statistics on mortality, morbidity, and risk factor levels in multiple developing countries (e.g., through sentinel surveillance programs).
2. Use available information on the importance of conventional risk factors (tobacco smoking, high BP, elevated lipids, etc.) to develop strategies for prevention in developing countries.
3. Encouraging national policies on agriculture (to make fruits and vegetables more affordable and promote the consumption of whole grains), urban planning (to promote physical activity during daily life) and effective tobacco control.
4. Performing large scale epidemiologic studies to document societal and individual factors influencing lifestyles and how these relate to risk factors and CVD.
5. Developing research capacity for investigating the determinants and modifiers of chronic disease such as CVD, obesity, and diabetes. Strengthening and improving the efficiency of existing national funding bodies for research. Raising the priority of chronic disease (including CVD), as being worthy of research funding by national and international organizations.
6. Encouraging and documenting the use of simple secondary prevention measures through registries and improving optimal prescribing through physician education programs.
7. Ensuring that proven therapies are affordable to those with CVD or for those with CV risk factors.
8. Raising awareness among the public of the health hazards of smoking, physical inactivity, and diets high in saturated fats and a high glycemic load.

From Yusuf S, Vaz M, Pais P: Tackling the challenge of cardiovascular disease burden in developing countries. Am Heart J 2004;148:1-4.

PHARMACOLOGIC INTERVENTIONS FOR PRIMARY PREVENTION

Aspirin

Several pharmacologic interventions have proven to be highly effective in the secondary prevention of cardiovascular disease. The role of aspirin in secondary prevention has been well-established. For example, the Antithrombotic Trialists' Collaboration showed that aspirin reduced the risk of cardiovascular events, myocardial infarction, and ischemic stroke in men and women.[312] Other meta-analyses also demonstrate

Table 9–12 Overview of Primary Prevention Trials of Aspirin Therapy

Study (Date and Reference Number)	Patients	Dose (mg)	Follow-Up	Cardiovascular Death: RR (95% CI)	Nonfatal Myocardial Infarction: RR (95% CI)	Nonfatal Stroke: RR (95% CI)
Physicians' Health Study (1988 #315)	22,071 men	325 on alternate days	5 yr	0.96 (0.80-1.14)	0.59 (0.47-0.74)	1.20 (0.91-1.59)
British Doctors' Trial (Peto, 1988 #318)	5139 men	500 mg daily	6 yr	0.93 (0.79-1.07)	0.97 (0.78-1.16)	1.13 (0.89-1.37)
Early Treatment of Diabetic Retinopathy Study (1992 #317)	3711 men and women	650 mg daily	5 yr	0.87 (0.70-1.10)	0.83 (0.66-1.04)	1.17 (0.79-1.28)
Thrombosis Prevention Trial (1998 #316)	5499 men	75 mg daily	6.4 yr	NA	0.68 (0.52-0.88)	NA
Hypertension Optimal Treatment Study (Hansson, 1998 #319)	18,790 men and women	75 mg daily	3.8 yr	0.95 (0.75-1.20)	0.64 (0.49-0.85)	0.98 (0.78-1.24)
Women's Health Study (Ridker, 2005 #321)	39,876 women	100 mg every other day	10 yr	0.95 (0.74-1.22)	1.02 (0.84-1.25)	0.83 (0.69-0.99)
Primary Prevention Trial (de Gaetano, 2001 #320)	4495 men and women	100 mg daily	3.6 yr	0.77 (0.62-0.95)	0.69 (0.38-1.23)	0.67 (0.36-1.27)

reductions in mortality and nonfatal CVD event rates among patients with prior MI, stroke, bypass surgery, angioplasty, peripheral vascular surgery, or angina.[313,314]

In primary prevention, randomized trials indicate that low-dose aspirin decreases the risk of a first myocardial infarction in men, with little effect on the risk of ischemic stroke, but the effects of aspirin appear to be different in women. Large-scale trials have assessed the benefits of low-dose aspirin in the primary prevention of CVD[315-320] and are shown in Table 9–12. In aggregate, among men, a summary of data from the Physicians Health Study, the British Doctors Trial, the Thrombosis Prevention Trial, the HOT study, and the Primary Prevention Project indicate that aspirin therapy is associated with a significant, 32% reduction in the risk of myocardial infarction (RR 0.68, 95% CI, 0.54 to 0.86; $P = 0.001$) and a nonsignificant increase in the risk of stroke (relative risk 1.13; 95% CI, 0.96 to 1.33; $P = 0.15$).[51]

By contrast, data from the Women's Health Study (WHS), of 39,876 initially healthy women 45 years of age or older who were randomized to receive 100 mg of aspirin on alternate days or placebo, demonstrated a nonsignificant reduction in CHD risk with aspirin compared with placebo (relative risk, 0.91; 95% CI, 0.80 to 1.03; $P = 0.13$).[321] There was a 17% reduction in the risk of stroke in the aspirin group compared with the placebo group (relative risk, 0.83; 95% CI, 0.69 to 0.99; $P = 0.04$). The latter was due to the net effect of a 24% reduction in the risk of ischemic stroke (relative risk, 0.76; 95% CI, 0.63 to 0.93; $P = 0.009$) and a nonsignificant increase in the risk of hemorrhagic stroke (relative risk, 1.24; 95% CI, 0.82 to 1.87; $P = 0.31$). Compared with placebo, aspirin had no significant effect on the risk of fatal or nonfatal myocardial infarction (relative risk, 1.02; 95% CI, 0.84 to 1.25; $P = 0.83$) or death from cardiovascular causes (relative risk, 0.95; 95% CI, 0.74 to 1.22; $P = 0.68$). Only in women older than age 65 did aspirin appear to significantly reduce the risk of major cardiovascular events, ischemic stroke, and myocardial infarction. In the same report, a meta-analysis of earlier studies was also performed, combining five large studies of aspirin with

Table 9–13 Guide to Cardiovascular Disease Risk Reduction in Apparently Healthy Patients

Risk Factor	Goal	Recommendations
Smoking	Complete cessation	Ask about smoking during routine evaluations. Encourage patient (and family members) to stop smoking. Provide counseling and information about enrolling in formal stop-smoking programs, offer access to nicotine replacement therapy/pharmacotherapy. Continue to evaluate.
High BP	<140/90 mm Hg	Measure BP in adults at least every 2 yr. Recommend healthy lifestyle practices, including weight control, increased physical activity, smoking cessation, and sodium restriction. If BP is 140/90 mm Hg after 3 mo of lifestyle modification or initial BP is 160/100 mm Hg, add antihypertensive medication to lifestyle modification.
High cholesterol	LDL-C <160 mg/dL if patient has 0-1 other risk factors,* <130 mg/dL if two or more risk factors; also HDL-C >40 mg/dL and TG <200 mg/dL	If LDL-C is elevated, rule out secondary causes such as liver or thyroid dysfunction. Begin Therapeutic Lifestyle Changes (diet: saturated fat <7% of calories, cholesterol <200 mg/day, carbohydrates 55% of calories, protein 15% of calories, polyunsaturated fat up to 10% of calories, monounsaturated fat up to 20% of calories; weight management; and increased physical activity). If target LDL (<130 mg/dL for patients with two risk factors; <160 for patients with 0–1 risk factors) is not met after 6 weeks, consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2 g/day) to enhance LDL lowering. If target LDL still not met after 6 more weeks, consider drug therapy. If HDL-C <40 mg/dL, emphasize weight management and physical activity. Consider niacin or fibrate if patient has two or more risk factors and elevated LDL-C.
Physical inactivity	30 min of moderate physical activity on most, if not all, days of the week.	Ask about routine physical activity and exercise habits. Encourage increased physical activity in daily life as well as a regular exercise program. Recommend medically supervised activities at least initially for patients with comorbidities or low functional capacity.
Weight	BMI <25 kg/m^2, waist circumference <40 inches for men and <35 inches for women; at a minimum, no increase in weight	Routinely measure patient's weight and height, as well as waist and hip circumferences.
Menopause		Combined estrogen plus progestin should not be used to prevent CVD in postmenopausal women
Antioxidants		Antioxidant supplements should not be used to prevent CVD pending trial results
Psychosocial	Evaluate for Depression/Anxiety Disorders. Assess structural/functional support.	Refer to programs/activities that will enhance social support and refer/treat depression/anxiety. Focus on management of overall stress and specific situations. Refer to programs/activities that will enhance social support and refer/treat depression/anxiety. Focus on management of overall stress and specific situations

*Risk factors include age (men ≥45 yr, women ≥55 yr or postmenopausal), smoking, hypertension, diabetes, family history of congestive heart disease in first-degree relative, and HDL-C <40 mg/dL. If HDL-C ≥60 mg/dL, subtract one risk factor.
BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
Adapted and modified from Grundy SM, Balady GJ, Criqui MH, et al: Guide to primary prevention of cardiovascular diseases. Circulation 1997;95:2329-31.

Table 9–14 Guide to Cardiovascular Disease Risk Reduction for Patients with Coronary and Other Vascular Disease or Diabetes

Risk Intervention	Goal	Recommendations
Smoking cessation	Complete cessation	Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, pharmacotherapy, and formal cessation programs as appropriate.
BP control	<140/90 mm Hg	Initiate lifestyle modification—weight control, physical activity, moderation of alcohol intake, moderation of sodium intake—in all patients with BP >140/90 mm Hg. Add BP medication if BP not <140/90 mm Hg in 3 mo or if initial BP >160/100 mm Hg, with therapy individualized to take into account patient requirements and characteristics, such as age and need for drugs with specific benefits; <130/80 if diabetic.
Lipid management	Primary goal: LDL-C ≤70 mg/dL. Secondary goal: HDL-C >40 mg/dL and TG <200 mg/dL	If LDL-C elevated, rule out secondary causes via liver function tests, thyroid function tests, and urinalysis. Begin Therapeutic Lifestyle Changes (diet: saturated fat <7% of calories, cholesterol <200 mg/d, carbohydrates 55% of calories, protein 15% of calories, polyunsaturated fat up to 10% of calories, monounsaturated fat up to 20% of calories; weight management; and increased physical activity; also consider increased soluble fiber (10-25 g/day) and plant stanols/sterols (2 g/day) to enhance LDL lowering in all patients. Assess fasting lipid profile. In post-MI patients, lipid profile may take 4-6 wk to stabilize. Add drug therapy according to the following guide: LDL-C >100 mg/dL—Add drug therapy to diet Drug selection modified according to TG level: TG <200 mg/dL—Statin TG >200 mg/dL—Consider combined therapy with statin plus either niacin or fibrate If LDL goal not achieved, consider combination drug therapy.
Physical activity	30 min of moderate physical activity on most, if not all, days of the week	Assess risk, preferably with exercise test, to guide prescription. Encourage a minimum of 30-60 min of moderate-intensity dynamic exercise 3-4 times/wk as well as increased physical activity in daily life. Maximum benefit from 5-6 h/wk. Advise medically supervised programs for moderate- to high-risk patients.
Weight management	BMI <25 kg/m^2, waist circumference <40 inches for men and <35 inches for women; at a minimum, no increase in weight	Start intensive diet and appropriate physical activity intervention, as outlined here, in patients >120% of ideal body weight for height. Emphasize the need for weight loss in patients with hypertension, elevated TG, or elevated glucose levels.
Glucose control	Near normal fasting glucose/HbA1C	First-step therapy: weight reduction and exercise; Second-step therapy: oral hypoglycemic agents; Third-step therapy: insulin
Menopause		Combined estrogen plus progestin should not be used to prevent CVD in postmenopausal women.
Antioxidants		Antioxidant supplements should not be used to prevent CVD pending trial results.
Psychosocial	Evaluate for depression/anxiety disorders. Assess structural/functional support.	Refer to programs/activities that will enhance social support and refer/treat depression/anxiety. Focus on management of overall stress and specific situations.

continued

Table 9–14 Guide to Cardiovascular Disease Risk Reduction for Patients with Coronary and Other Vascular Disease or Diabetes—cont'd

Risk Intervention	Goal	Recommendations
Antiplatelet agents/ anticoagulants	Unless contraindicated, start aspirin at 80-325 mg/d. Start clopidogrel if patient is intolerant to aspirin.	Manage warfarin to international normalized ratio of 2-3.5 for post-MI patients unable to take aspirin. Consider warfarin in patients with severe LVD.
Angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin-receptor blockers		Start as soon as possible after MI in stable patients if hemodynamics tolerate. Use angiotensin-receptor blockers if intolerant to ACEI.
β-Blockers		Start in post-MI patients and continue indefinitely if hemodynamics tolerate.

BMI, body mass index; BP, blood pressure; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; MI, myocardial infarction; TG, triglycerides.
Adapted and modified from Smith SC Jr, Allen J, Blair SN, et al: AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: Endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363-2372.

the WHS study findings. Aspirin therapy reduced the risk of myocardial infarction (RR 0.76, 95% CI, 0.62 to 0.95, $P = 0.01$) and there was no reduction in stroke endpoints among men and women (RR 0.97, 95% CI, 0.83 to 1.13, $P = 0.69$). However, in analyses that included only women that used combined data from the Women's Health Study, the Hypertension Optimal Treatment (HOT) study, and the Primary Prevention Project, aspirin therapy was associated with a significant 19% reduction in risk of stroke (RR 0.81; 95% CI, 0.69 to 0.96; $P = 0.01$), but no reduction in risk of myocardial infarction (relative risk, 0.99; 95% CI, 0.83 to 1.19; $P = 0.95$).

Future Questions About Aspirin Therapy

Although the benefits of aspirin use for secondary prevention are solid, in primary prevention, the evidence supports only benefit in men, and among women older than the age of 65. The Preventive Services Task Force[322] and the American Heart Association[120] recommend aspirin for adults whose 10-year risks of a first coronary event are >6% and 10%, respectively. Aspirin should be used in most patients with cardiovascular disease.

Because differing doses of aspirin have been used in different trials, the correct dose for CHD prevention remains to be elucidated. Whether particular subgroups—diabetic, hypertensive—have different benefits from aspirin therapy also needs to be assessed. Antiplatelet agents such as ticlopidine and clopidogrel may be used in patients with aspirin allergy or intolerance.

β-Blockers

The role for β-blockers in secondary prevention after myocardial infarction has been long established[74] with important benefits post-myocardial infarction[323-326] and in the setting of acute myocardial infarction.[327,328] Primary prevention data regarding primarily β-blockers pertain to the treatment of hypertension, a major risk factor for cardiovascular disease. In the Puget Sound case-control study, the relative risk of hospitalization or death due to coronary heart disease was reduced by 29% in hypertensive heart patients treated with β-blockers compared with controls.[329] Also, in the British DHSS Hypertension Care Computing Project, men on β-blockers had lower mortality rates.[330] Although β-blockers are important for the treatment of hypertension and are also effective in preventing CVD, whether their effects are due to specific properties of β-blocker therapy including arrhythmia suppression, neurohumoral activity or to blood pressure management is undetermined.

ACE Inhibitors

ACE inhibitors (ACEI) are important agents for decreasing mortality after myocardial infarction,[331-333] particularly in patients with low ejection fraction (EF).[334] The benefits of ACEI in asymptomatic patients post-myocardial infarction with EF <40% were reported by the SAVE study, wherein long-term administration of captopril was associated with a 19% risk reduction in mortality.[93] Subsequently, the Heart Outcomes Prevention Evaluation (HOPE) Study demonstrated that the benefit of ACE inhibitors could be extended to patients with coronary heart disease and diabetes without left ventricular dysfunction.[80]

In primary prevention studies, ACE inhibitors have not been shown to be superior to other medical agents for the reduction of hypertension. For example, in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial,[87] ACE inhibitors, calcium channel blockers, and diuretics showed similar effects on blood pressure management.

PRACTICE OF PREVENTIVE CARDIOVASCULAR DISEASE

Because worldwide the prevalence of CVD continues to rise, particularly in the developing world, strategies aimed at controlling this epidemic must target populations to achieve substantial reductions in disease burden. According to NHANES

data, in the United States alone, it is estimated that among those persons without a history of MI or stroke, but two or more inadequately controlled CVD risk factors, the population-attributable risk of CVD is 14% (approximately 17% of the U.S. population) and the annual cost is 13.2 billion dollars.[335] This cost is similar to that incurred by those individuals who already have a history of CVD. The cost of inadequate primary and secondary preventive efforts for CVD represents 30.1 billion dollars or 3% of the health care budget. Because these data do not take into account diabetes, this number may be an underestimate. In England, it is also estimated that if aggressive treatment strategies were instituted for those persons with a >20% 10-year Framingham Cardiovascular risk, major CVD events would be reduced by 34%.[336]

The effectiveness of any preventive medicine practices is highly dependent on population size and the number of targeted risk factors. A number of studies suggest that gain in years of life-expectancy is higher at younger ages, for male sex, and with treatment of those persons with risk factor clustering.[337] Tables 9–13 and 9–14 present information on the prevention of CVD for different patient categories. To reduce the staggering burden of CVD, efforts aimed at (1) understanding and improving barriers related to population and care-giver education about CVD and (2) uniform adherence to recommended therapy are warranted. These efforts must be coupled with community-based programs that incorporate nonphysician caregivers as well as continued risk factor research efforts in all populations.

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Chapter 10

Non ST-Elevation Acute Coronary Syndromes

Stephen D. Wiviott and Robert P. Giugliano

CHAPTER CONTENTS

In this chapter we have drawn from evidence-based guidelines, have adopted the standard classification schemas used to grade the level of recommendation and strength of supportive evidence, and have provided updated information from the literature.[1-5] Because many of the supportive studies focused on a single comparison (e.g., drug X versus drug Y or drug X versus placebo) rather than comparisons of complex treatment strategies, and because the elderly and women are generally under-represented in published clinical trials, the reader should consider the impact of generalizing such results from specific studies to their patients.

Integrative Risk Assessment

Many attempts have been made to integrate clinical predictors and to objectify the assessment of the probability of adverse outcomes in different patient populations using multivariable analysis. Efforts have been made to incorporate physiologic, laboratory and demographic characteristics of patients into risk scores such as the Thrombolysis in Myocardial Infarction (TIMI) risk score for unstable angina/non ST-segment elevation myocardial infarction (UA/NSTEMI). Other scores derived from clinical trials[6,7] and registries[8-10] were developed to assess the risk of patients with non ST-segment elevation—acute coronary syndrome (NSTE-ACS) and to help identify patients most likely to benefit from aggressive therapy. An analysis comparing three risk scores (the TIMI, PURSUIT and GRACE scores, Table 10–1)[11] concluded that all three demonstrated good predictive accuracy for death or MI. The TIMI Unstable Angina Risk Score has been found to be useful in the prediction of angiographic severity and the extent of coronary artery disease,[12] including greater intracoronary thrombus burden and impaired flow.[13] Patients with higher TIMI risk scores derive greater benefit from aggressive antithrombotic strategies[14,15] and an early invasive strategy of angiography and coronary intervention.[16]

ANTI-ISCHEMIC MEDICATIONS

Management of UA/NSTEMI should be directed toward the dual goals of relief of the symptoms of myocardial ischemia and prevention of the severe short- and long-term sequelae that include recurrent MI, congestive heart failure, and death. Therapeutic efforts should be focused intensely on therapies that achieve both of these goals. A multi-faceted and continuously updated approach to the management of patients with NSTE-ACS may be necessary. For instance, a medication such as nitroglycerin, that may be used on the first encounter with a patient with ongoing ischemic chest pain to provide symptomatic relief, may be replaced with agents, such as angiotensin-converting enzyme inhibitors, that are expected to modify long-term risk. Patients for whom initial, intensive pharmacologic therapy does not produce relief of ischemic symptoms should be considered as candidates for early cardiac catheterization and revascularization (or ischemic relief with mechanical therapies such as intra-aortic balloon counterpulsation). For the majority of patients with NSTE-ACS, relief of ischemic symptoms can be achieved with pharmacologic measures.

Myocardial ischemia is a consequence of an imbalance in myocardial oxygen supply and demand. In most cases of UA/NSTEMI, the principal cause of this imbalance is abrupt reduction of blood flow resulting from nonocclusive coronary thrombosis.[17] For this reason, mainstays of therapy for UA/NSTEMI include antithrombotic and antiplatelet therapies, and coronary revascularization.[1] Revascularization may not always be immediately available, practical, safe or appropriate, and pharmacologic management of myocardial oxygen demand (MVO_2), and to a lesser extent supply, may result in relief of symptoms. The principal components of MVO_2 are heart rate, myocardial contractility, and wall stress.[18] Controlling and reducing these factors helps to improve the balance and relieve angina. Major classes of antianginal therapy include nitrates, β-adrenergic receptor antagonists (β-blockers), and calcium channel blockers. Morphine sulfate has mixed effects that reduce oxygen demand and angina.

Nitrates

The use of nitrates in NSTE-ACS is based on physiologic principles and expert consensus.[1] Nitroglycerin should be used in UA/NSTEMI for the rapid relief of ischemia and

Table 10–1 Integrative Clinical Risk Scores for Unstable Angina/Non ST-Segment Elevation Myocardial Infarction

Score	Features	Comments
TIMI[6]	Age ≥65, ≥3 cardiac risk factors, aspirin use in last 7 days, known CAD (previous stenosis ≥50%), recurrent angina in last 24 h, ST-segment deviation, elevated markers of necrosis	Sum of number of features (1 point for each)
PURSUIT[7]	Age by decade, sex, worst CCS class in last 6 weeks, signs of heart failure, ST-depression	Weighted score based on different point total (ranging from 0-14) for each feature
GRACE[9]	Age, heart rate, systolic BP, creatinine, Killip class, cardiac arrest, elevated markers, ST-segment deviation	Weighted score based on different point total (ranging from 0-91) for each feature.

BP, blood pressure; CAD, coronary artery disease; CCS class, Canadian Cardiovascular Society Anginal Class.

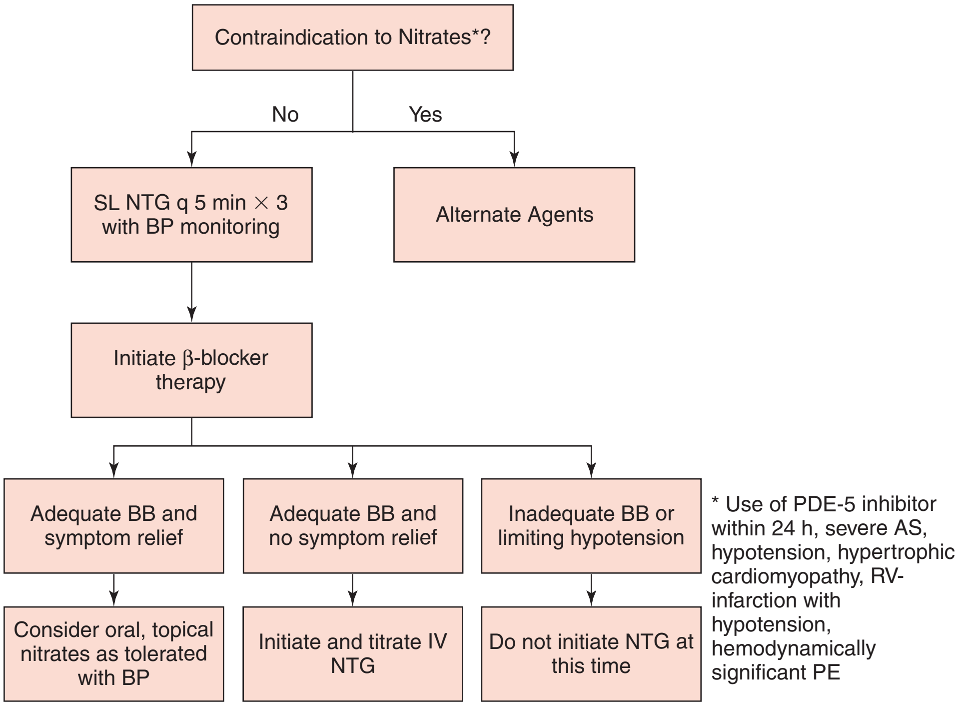


Figure 10–1 Schematic for early use of nitrates in acute coronary syndrome. AS, aortic stenosis; BB, β-blocker; BP, blood pressure; NTG, nitroglycerin; PE, pulmonary embolism; RV, right ventricular; SL, sublingual.

ischemic-related symptoms including angina and congestive heart failure (Fig. 10–1). In suitable patients, nitrate administration should begin with sublingual administration of 0.4 mg (tablets or spray) given at 5-minute intervals up to three doses. Intravenous nitroglycerin treatment may be initiated in patients with refractory symptoms and without hypotension despite adequate doses of β-blocker.[1] Intravenous nitroglycerin is initiated at 5 to 10 mcg/min of continuous infusion and may be titrated upward at 3- to 5-minute intervals until 20 mcg/min is reached. If this dose is tolerated without hypotension and anginal symptoms persist, larger titration steps of 20 mcg/min are usually well tolerated. Titration should cease when symptom relief is achieved, when hypotension ensues, or when a maximum dose of approximately 200 to 300 mcg/min is reached. Tolerance to the anti-ischemic effects of nitrates may develop within 12 to 24 hours and can be ameliorated by nitrate-free intervals. If symptoms do not allow for nitrate-free intervals, increasing the dosing may be effective. Despite tolerance, abrupt removal of nitrates may result in recurrent ischemia,[19] and discontinuation of high-dose intravenous nitrates should be performed by stepped down-titration.

The pharmacologic effects of nitrates, predominantly venodilation and reduction of ventricular preload, may be detrimental to patients who are highly dependent on ventricular preload for the maintenance of cardiac output and can result in substantial hypotension. Nitrates should generally be avoided, or used with considerable caution, in patients with right ventricular infarction, severe aortic stenosis, hypertrophic cardiomyopathy, or pulmonary embolism. Nitrates are contraindicated in patients who have used phosphidiesterase-5 (PDE-5) inhibitors (sildenafil, tadilafil, vardenafil) within the preceding 24 to 48 hours[1] because of exaggeration and prolongation of nitrate effects from the inhibition of the breakdown of cyclic GMP, which modulates the vasodilator effects of nitrates. The combination of PDE-5 inhibitors and nitrates has been reported to be associated with severe hypotension, myocardial ischemia, and death.[20,21]

β-Adrenergic Receptor Blockers

Clinical trial data for the use of β-blockers specifically in UA/NSTEMI are sparse. A systematic review of the accumulated trial data suggests that β-blockers reduce the risk of progression to MI in NSTE-ACS.[22] In contrast, a large body of randomized controlled trial data suggests benefits in reducing recurrent MI and death by early β-blocker use in STEMI.[23-25] Therefore, the evidence for the use of β-blockers in NSTE-ACS results largely from extrapolation from STEMI trials and physiologic principles.

Based on these data, β-blockers should be initiated in the treatment of UA/NSTEMI as early as possible for patients without contraindications. β-blockers should be used cautiously or avoided in patients with new or decompensated congestive heart failure or significant first-degree atrioventricular block, and withheld in patients with severe bradycardia, second-, or third-degree AV block without a pacemaker, and selective β-blocker patients for whom NSTE-ACS is secondary to profound catecholamine excess, such as pheochromocytoma or cocaine use. For patients with reactive airways disease, the use of a cardioselective (β_1) agent is recommended. Initial therapy for patients with evidence of ongoing ischemia should be intravenous β-blocker such as metoprolol 5 mg every 5 minutes up to three doses as tolerated by heart rate and blood pressure. After initial IV dosing, oral β-blocker therapy should be initiated early to avoid a rebound effect between the offset of the IV agent and the onset of the oral agent.

Calcium Channel Antagonists

Dihydropyridine calcium channel blockers have predominantly peripheral vasodilatory actions, whereas nondihydropyridine CCBs have significant SA- and AV-node depressant effects as well as possible myocardial depressant effects with lesser amounts of peripheral vasodilation (see Chapter 5). Coronary vasodilation appears to be similar among agents.[1] The predominant clinical role for CCBs has been in the control of hypertension. However, the physiologic properties of arterial vasodilation, heart rate slowing, and contractility reduction favorably alter myocardial oxygen balance. Because of these differences in properties, the two types of CCBs will be considered separately.

The dihydropyridine CCBs cause a reflex tachycardia in the absence of adequate β-blocker therapy, a mechanism that may underlie apparent adverse effects of these agents on patients with NSTE-ACS.[26,27] In contrast to the dihydropyridines, diltiazem and verapamil are heart rate slowing agents and appear not to increase rates of ischemic events in patients with UA/NSTEMI. Concerns, however, have been raised that myocardial depressant effects may increase the risk of heart failure. The relationship of the nondihydropyridine CCBs to congestive heart failure is somewhat controversial. In retrospective analyses of calcium channel blocker trials, there has been evidence for increased rates of congestive heart failure and an increase in the mortality rate in patients with diminished ejection fraction.[28,29] These findings, however, are counterbalanced by studies that show beneficial effects of CCBs in patients with heart failure who are treated concurrently with ACE inhibitors.[30]

In summary, calcium channel blockers reduce symptomatic ischemia. Short-acting dihydropyridine CCBs have not been shown to improve cardiac outcomes and may result in worse outcomes in the absence of β-blockers. Newer, longer acting dihydropyridine CCBs have not been studied in NSTE-ACS. Nondihydropyridine calcium channel blockers are antianginal, do not result in harm, and may improve outcomes in patients with NSTE-ACS, especially those patients without left ventricular dysfunction. Therefore, nondihydropyridine calcium channel blockers can be considered for use in patients who do not tolerate β-blockers.[1]

ANTIPLATELET AGENTS

Antiplatelet agents represent the cornerstone of therapy for patients with NSTE-ACS. Pharmacologic inhibition of platelet function can be achieved by interfering with a number of processes that include inhibition of cyclooxygenase (COX), phosphodiesterase, adenosine diphosphate (ADP), thromboxane, serotonin, platelet adhesion, or platelet aggregation, and has led to the development of numerous platelet inhibitors (Table 10–2), of which aspirin, the thienopyridines, and the intravenous glycoprotein (GP) IIb/IIIa inhibitors have been studied most extensively.

Table 10–2 Classification Scheme of Select Antiplatelet Agents

Arachidonic Acid Inhibitors

Cyclooxygenase (COX) inhibitors—aspirin, indobufen, triflusal, nonsteroidal anti-inflammatory agents, sulfinpyrazone

Non-COX inhibition of arachidonic acid

Phosphodiesterase Inhibitors—dipyridamole, pentoxifylline, cilostazol, trapidil

Other—omega-3 fatty acids, eicosanoids (prostacyclin, prostaglandin analogs)

$P2Y_{12}$ Inhibitors

Thienopyridines (ADP antagonists)—ticlopidine, clopidogrel, prasugrel

ATP derivative—cangrelor

Cyclopentyltriazolopyrimidine (CPTP)—AZD6140

Inhibitors of Platelet Adhesion

von Willebrand factor (vWF) inhibitors—aurintricarboxylic acid (ATA), peptide fragments derived from the human plasma vWF-GP1b-IX binding domain, monoclonal antibodies to vWF

GP1b-IX Inhibitors

Platelet Glycoprotein IIb/IIIa Receptor Blockers

Intravenous

Abciximab, tirofiban, eptifibatide

Oral

Xemilofiban, sibrafiban, orbofiban, lotrafiban, roxifiban, cromofiban

Drugs with Secondary Antiplatelet Activity

Direct thrombin inhibitors, heparin, nitrates, fibrates, calcium-channel antagonists, and others

Aspirin

Several small- to medium-sized clinical trials that compared aspirin with placebo in NSTE-ACS demonstrated approximately a 50% reduction in death or MI (Fig. 10–2). These data support the class I indication in the 2002 ACC/AHA UA/NSTEMI Guideline Update to begin aspirin immediately and to treat indefinitely on establishment of the diagnosis of NSTE-ACS.[3] Because aspirin is one of the most inexpensive drugs available, with a known and generally safe profile, it is unlikely that future placebo-controlled studies will be undertaken, and thus aspirin is likely to remain the first-line antiplatelet agent in NSTE-ACS for the foreseeable future.

Two areas of intense debate and ongoing research regarding aspirin use are the issues of optimal dose and aspirin resistance. Despite its long history, the optimal dose of aspirin remains to be definitively established. Increased doses have been associated with more bleeding, yet the relationship of the dose with efficacy is less clear.[31] A dose of 40 mg was found to achieve maximal inhibition once steady state has been achieved, although doses of >160 mg are needed to produce a rapid clinical antithrombotic effect, and doses of <75 mg daily have not been well studied in clinical trials.[32-35] A meta-analysis by the Antiplatelet Trialists' Collaboration demonstrated no increase in benefit in aspirin across maintenance doses ranging from 75 mg to 1500 mg daily, whereas gastrointestinal bleeding *was* increased at doses above 300 mg daily.[31] Two nonrandomized subgroup analyses[36,37] comparing different doses of aspirin confirmed that higher doses of aspirin were associated with an increased risk of bleeding and no apparent reduction in ischemic complications. A random effects multivariate regression model concluded that efficacy of aspirin did not increase at higher doses; in fact, the point estimates suggest less benefit at higher doses.[38]

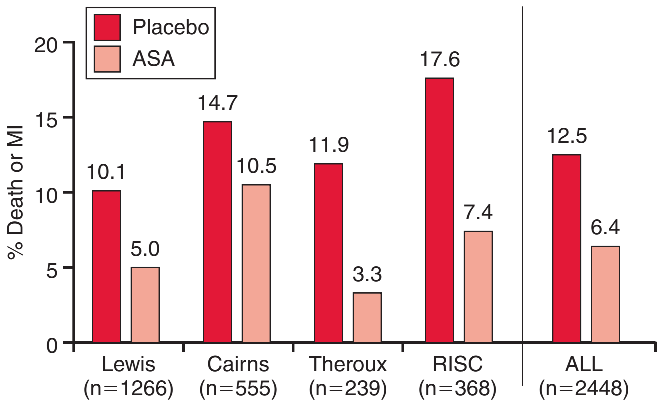


Figure 10–2 Placebo-controlled trials with aspirin in patients with non ST-segment elevation acute coronary syndrome (NSTE-ACS). Aspirin was associated with a 50% reduction in death or MI compared with placebo. (From Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA guideline update for the management of patients with unstable angina and non ST-segment elevation myocardial infarction—2002: Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on the Management of Patients with Unstable Angina]. Circulation 2002; 106(14):1893-1900.) (With permission).

An inadequate response to aspirin, sometimes termed "aspirin resistance," has been described for more than a decade.[39] Controversy persists, however, regarding how this should be defined and what methodology should be used to measure the antiplatelet effect of aspirin.[40] Several studies have shown that resistance to aspirin is associated with worse clinical outcomes across a broad range of patients with stable and unstable CAD, peripheral vascular disease, and stroke (Table 10–3). There are multiple possible explanations for hyporesponsiveness to aspirin, including clinical factors (e.g., noncompliance, failure to absorb the drug), cellular factors (e.g., failure to suppress COX, increased platelet activation), and genetic polymorphisms involving key enzymes (e.g., COX-1) or receptors (GP-IIIa). Three clinical factors that have been associated with hyporesponsiveness to enteric-coated aspirin 81 mg are younger age, increased weight, and history of MI.[41] Increasing the dose of aspirin may increase the antiplatelet response in such patients; whether this improves clinical outcomes has yet to be demonstrated.

Guidelines for patients with NSTE-ACS[1,42] or who are undergoing PCI[43] recommend an initial dose of 162 mg to 325 mg. Post-stenting, the recommended dose is 325 mg for at least 1 month (bare metal stent), 3 months (sirolimus-coated stent), or 6 months (paclitaxel-coated stent).[43] To decrease the risk of bleeding, the aspirin dose may be reduced to 81 mg to 162 mg.[43]

Thienopyridines

Thienopyridines act by irreversibly blocking the $P2Y_{12}$ receptor on the platelet surface, thereby interrupting platelet activation and aggregation.[44] When administered at the currently approved doses (clopidogrel 75 mg daily, ticlopidine 250 mg twice daily), these agents achieve at steady state a moderate level of median platelet inhibition (20% to 35%)[45,46] as assessed by using 20 μmol/L ADP as the agonist, compared with the intravenous GP IIb/IIIa inhibitors (80% to 95%).[47] An earlier effect on platelet function occurs with administration of a loading dose,[48] although the absolute degree of platelet inhibition is marginally increased with higher doses once steady state is achieved. Bleeding time increases roughly twofold and normalizes 10 days after the last dose, consistent with the life span of the platelet. The thienopyridines also have

Table 10–3 Clinical Impact of Resistance to Aspirin

Patient Cohort	Aspirin Dose	Duration of Follow-up	Endpoint	Result (resistant vs. responsive groups)
Stroke[1]	1500 mg	24 months	Stroke/MI/vascular death	10-fold ↑
PVD[2]	100 mg	18 months	Arterial occlusion	87% ↑
CVD/CVA/TIA[3]	100 mg	>60 months	Recurrent CVA/TIA	34% vs. 0%
HOPE subgroup[4]	75-325 mg	5 years	MI/stroke/CV death	1.8-fold ↑ (1st vs. 4th quartile)
CVD[5]	325 mg	~2 years	Death/MI/CVA	3-fold ↑

a number of other effects that are not fully characterized on platelet function beyond inhibition of ADP-induced aggregation, such as inhibition of platelet activation, reduction in fibrinogen levels and blood viscosity, and less erythrocyte deformability and aggregability. If rapid onset of platelet inhibition is required (e.g., at the time of intracoronary stenting), a loading dose should be administered (Table 10–4).

Based on the CAPRIE study that demonstrated about a 9% reduction compared with aspirin in vascular death, MI, or stroke among 19,185 patients with atherosclerotic vascular disease, clopidogrel was given a class I recommendation for use in patients with NSTE-ACS who have hypersensitivity or major gastrointestinal intolerance to aspirin.[49] The combination of aspirin plus clopidogrel was compared with aspirin alone in the CURE trial of 12,562 patients with NSTE-ACS treated for 3 to 12 months.[50] Clopidogrel reduced the composite of death, MI, and stroke by 20% compared with placebo, with benefit evident both in the first 30 days and over the ensuing average follow-up of up to 9 months.[51] There was also a 38% increase in the rate of bleeding overall, with patients who underwent CABG within 5 days of the discontinuation of clopidogrel at particular risk (53% increased rate). In a secondary analysis (PCI-CURE) of patients in the CURE trial who underwent percutaneous coronary intervention (PCI), patients pretreated with clopidogrel (for a median of 10 days) had a reduction in both early (30-day) and long-term cardiovascular events.[52] As a result of these findings, the 2002 ACC/AHA UA/NSTEMI guidelines[3] considered the use of clopidogrel in addition to aspirin to have a class I indication for patients with NSTE-ACS who are undergoing an early noninterventional or interventional approach and who are not at risk for major bleeding. For patients for whom elective CABG is planned, the drug should be withheld for 5 to 7 days to reduce the risk of perioperative bleeding and transfusion.

Several important issues regarding treatment with clopidogrel remain controversial and continue to be studied: identification of the optimal loading dose and timing of initiation of clopidogrel, duration of therapy, and clinical relevance of clopidogrel resistance. Without a loading dose, clopidogrel achieves steady-state levels of platelet inhibition in 4 to 7 days. Administration of various loading doses has been studied, with reductions in the time to steady state of 12 to 48 hours (for 300 mg) to 2 to 6 hours (for 600 to 900 mg). Data from the CREDO trial[53] suggested that a minimum of 12 to 15 hours between the loading dose and PCI was required for a 300 mg load to demonstrate clinical benefit (compared with no load), whereas the ARMYDA-2 study[54] showed better outcomes with 600 mg versus 300 mg when clopidogrel was initiated 4 to 8 hours before PCI (Fig. 10–3). The decisions to load or not before PCI, and with what dose, are clinically important because of the trade-off between potential benefit (if a sufficient load is administered long enough before PCI) and risk of bleeding (if the patient needs to undergo CABG surgery). Given the limited amount of available clinical data (both CREDO and ARMYDA-2 were relative small trials, the latter had an unusually high event rate in the 300 mg clopidogrel arm), it is not surprising to find divergent recommendations in the two PCI guidelines released in 2005[43,55,56] and divergent practice patterns in Europe and North America. The European Society of Cardiology guidelines recommend 300 mg of clopidogrel ideally administered the day before PCI and 600 mg administered if PCI is being performed within 6 hours.[55] Meanwhile, the ACC/AHA/SCAI guideline takes a more conservative position, recommending that a 300-mg dose be administered at least 6 hours before the procedure, noting that the clinical benefit and safety of higher doses of clopidogrel are not well established.[43]

The duration of treatment with clopidogrel is an important clinical issue because the drug is costly to administer relative to aspirin and is associated with an increased risk of bleeding. The primary endpoint in the CURE study was at 30 days and a secondary endpoint was at the end of the trial (mean 9 months, range 3 to 12 months). The AHA/ACC NSTE-ACS guideline[3] currently gives a class Ia indication to a treatment duration of 1 month, with 9 months' duration considered class Ib. After PCI, the optimal duration of clopidogrel therapy depends on the risk of subsequent thrombosis, which itself is a related to the type of intervention, use of an intracoronary stent, and the type of drug-eluting stent (if any) placed (Table 10–5). These recommendations are based largely on observational data and randomized trial protocols (as opposed to randomized comparisons); further studies are

Table 10–4 Standard Dosing Regimens for Frequently Used Antiplatelet Agents

Drug	Loading Dose	Maintenance Dose
Aspirin	162-325 mg PO* or p.r. 150-500 mg IV	75-325 mg daily PO indefinitely
Thienopyridienes		
Clopidogrel	300-600† mg PO	75 mg PO daily for ≥ 30 d
Ticlopidine	500 mg PO	250 mg twice PO daily for ≥ 30 d
Glycoprotein IIb/IIIa Blockers		
Abciximab	0.25 mg/kg IV	0.125 mcg/kg/min IV for 12-24 h
Eptifibatide	180 mcg/kg IV‡	2§ mcg/kg/min IV for 18-72 h
Tirofiban	0.4‖ mcg/kg/min IV × 30 m	0.1‖ mcg/kg/min IV for 48-96 h

*Preferably chewed to achieve more rapid absorption.
†Some studies have investigated 900 mg but few, if any, clinically meaningful differences have been reported between 600 mg and 900 mg.
‡In patients scheduled to undergo PCI, a second bolus of 180 mcg/kg IV is given 10 minutes after the first bolus.
§1 mcg/kg/min if the estimated creatinine clearance is <50 mL/min.
‖The loading and maintenance infusion rates should be reduced by one half if the estimated creatinine clearance is <30 mL/min.

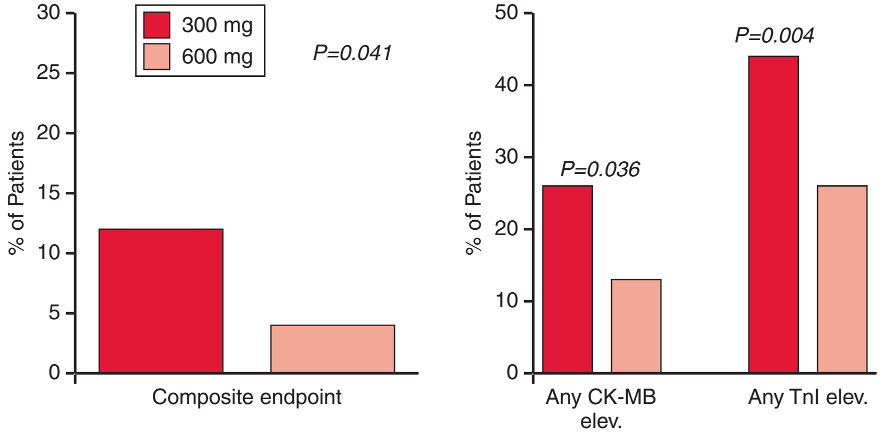


Figure 10–3 Main results of the ARMYDA-2 trial. ARMYDA-2[54] compared 600 mg with 300 mg clopidogrel administered 4 to 8 hours before PCI in 255 patients with known CAD. The rate of the primary composite endpoint of death, MI, or target vessel revascularization up to 30 days post-PCI, as well as the rates of elevated biomarkers of myonecrosis post-PCI, were reduced with clopidogrel 600 mg. The rate of MI following PCI with 300 mg was unexpectedly higher than has been reported in other similar studies. CAD, coronary artery disease; CK-MB elev., creatine kinase-myocardial band elevation; MI, myocardial infarction; PCI, percutaneous coronary intervention; TnI elev., troponin I elevation. (With permission).

Table 10–5 Minimum Duration of Recommended Uninterrupted Clopidogrel Therapy in Patients with Non ST-Segment Elevation-Acute Coronary Syndrome

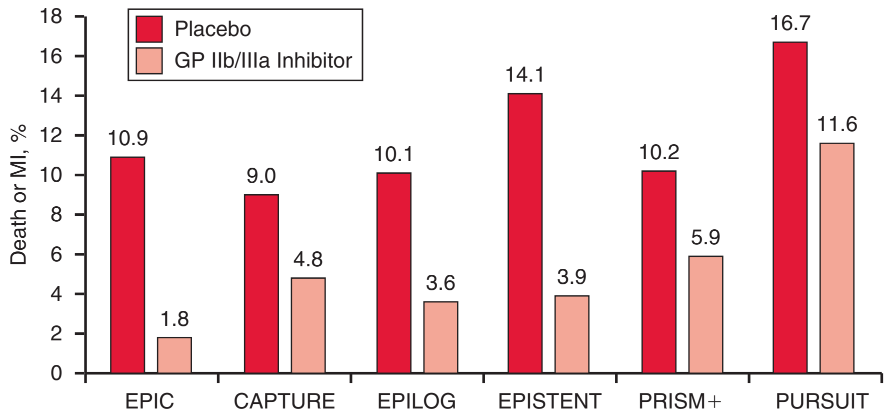
Patient Scenario	Minimum Recommended Duration
NSTE/ACS managed without stenting	1 month
Bare metal stent	1 month*
Sirolimus-coated stent	3 months
Paclitaxel-coated stent	6 months
Stent brachytherapy	Indefinitely

*2 weeks acceptable if patient at substantially increased risk of bleeding.
NSTE-ACS, non ST-segment-acute coronary syndrome.
Modified from Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al: ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). Circulation 2006;113:156-75.

awaited. Other observational data have identified a strong link between the interruption of antiplatelet therapy after ACS[57] and an increased risk of adverse outcomes including stent thrombosis.[58] Thus, the threshold to hold or terminate antiplatelet therapy early should be high (e.g., life-threatening bleeding or need for high-risk emergency surgery).

The CHARISMA trial evaluated the usefulness of clopidogrel in addition to aspirin for a median of 28 months in high-risk patients with stable cardiovascular disease across a wide range of patients.[59,60] Although there was no difference in the primary endpoint of cardiovascular death, MI, or stroke between the clopidogrel plus aspirin group (6.8%) and the placebo plus aspirin group (7.3%, $P = 0.22$), the secondary endpoint (which also included rehospitalization for ischemic events) was reduced by 8% ($P = 0.04$) with dual antiplatelet therapy.[61] The secondary prevention subgroup (approximately 80% of patients enrolled had documented preexisting cardiovascular disease) had a 12% ($P = 0.046$) lower incidence of the primary composite, whereas the remainder of asymptomatic patients (primary prevention) had a 20% excess ($P = 0.20$), including a higher rate of cardiovascular death (3.9% versus 2.2%, $P = 0.01$). In the overall study population, severe bleeding tended to be more frequent in the clopidogrel group (1.7% versus 1.3%, $P = 0.09$). Thus, longer-term clopidogrel, in addition to aspirin, appeared beneficial in secondary prevention of ischemic complications among patients with established cardiovascular disease (with a trend toward more severe bleeding), but was not useful and potentially harmful in asymptomatic patients (primary prevention).

Failure of clopidogrel to achieve the desired pharmacologic effect is another area that is undergoing intense research. Several studies of platelet function have documented the variable pharmacologic response to standard dose clopidogrel among groups of individuals. Depending on the method, timing, and definition of "resistance," between 5% and 30% of patients do not achieve the expected pharmacologic response to clopidogrel.[62,63] This may be overcome, in part, by either readministration of a 300-mg loading dose to patients who were chronically taking 75 mg daily,[64] or by loading initially with 600 mg in clopidogrel naïve patients.[65] This may come at a cost of increased bleeding risk particularly in patients who subsequently require urgent CABG. Similar to the observations described with resistance to aspirin, several small studies have suggested that hyporesponders to clopidogrel are at increased risk of ischemic complications, including stent thrombosis.[65-67] Pending confirmation of these findings in larger datasets, two important questions need to be answered: (1)should antiplatelet effect be routinely measured—and if so—how?; (2) how can clopidogrel resistance be minimized or managed?[68] Among the possible options to achieve higher degrees of inhibition of platelet aggregation are intravenous GP IIb/IIIa inhibitors and newer inhibitors of the $P2Y_{12}$ receptor (see Antiplatelet Drugs in Development).



	EPIC	CAPTURE	EPILOG	EPISTENT	PRISM+	PURSUIT
P-value	0.001	0.003	<0.001	0.001	>0.05	0.01
RR ↓	83%	47%	64%	72%	42%	31%
Abs risk ↓	9.1%	4.2%	6.5%	10.2%	4.3%	5.1%
N, PCI	321	1265	1328	335	475	1228
Drug	← Abciximab			→	Tirofiban	Eptifibatide

Figure 10–4 Intravenous GP IIb/IIIa inhibitors in patients with NSTE-ACS undergoing percutaneous coronary intervention (PCI). The outcome of death or myocardial infarction in six clinical trials of intravenous GP IIb/IIIa inhibitors that involve more than 1000 patients is shown. (From Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non ST-Segment Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on the Management of Patients with Unstable Angina]. Available at: http://www.acc.org/clinical/guidelines/unstable/unstable/pdf.) (With permission).

Intravenous Glycoprotein IIB/IIIA Blockers

The most potent inhibitors of platelet aggregation clinically available are the intravenous GP IIb/IIIa blockers. These agents inhibit the final common pathway of platelet aggregation, namely, the binding of fibrinogen or von Willebrand factor to the membrane GP IIb/IIIa integrin receptor, thus preventing the inducement of platelet aggregation by various platelet agonists. There are three intravenous GPIIb/IIIa blockers commercially available: abciximab (an irreversible monoclonal antibody), eptifibatide, and tirofiban (the latter two are reversible small molecules). Several oral GP IIb/IIIa blockers were studied in clinical trials; however, their development was halted after five consecutive phase III studies demonstrated an increase in mortality rate.[37,69] We will, therefore, focus the remainder of this section on the intravenous preparations.

Intravenous GP IIb/IIIa blockers were initially developed for use as adjuncts to PCI, and numerous clinical trials have demonstrated reductions in ischemic complications (particularly periprocedural MI) with their use. In six large trials of patients with NSTE-ACS who were undergoing PCI, the relative risks of death or MI at 30 days were reduced by 31% to 83% with the addition of intravenous GP IIb/IIIa inhibitors (Fig. 10–4).[1] It is estimated that intravenous GP IIb/IIIa inhibitors may reduce mortality by one third across a wide range of patients who were undergoing PCI.[70] These data support the current class Ia indication for intravenous GP IIb/IIIa blockers in patients with NSTE-ACS for whom an early invasive strategy is planned (Table 10–6).[1,42]

Among patients with NSTE-ACS who are *not* routinely scheduled to undergo coronary revascularization, a meta-analysis involving 31,402 patients demonstrated a smaller reduction in the odds of death or MI (9% [2% to 16%], $P = 0.015$) with addition of intravenous GP IIb/IIIa inhibitor therapy.[71] However, there was evidence for heterogeneity by drug because the largest trial (GUSTO-IV ACS[72]) with abciximab (which does not sustain a high degree of platelet inhibition beyond 12 hours) showed a directionally negative effect, whereas trials with the small molecule intravenous GP IIb/IIIa blockers revealed modest benefits. Furthermore, post-hoc analyses demonstrated greater benefit among patients who are at higher risk at baseline, as identified by an elevated baseline troponin[71] or higher TIMI Risk Score.[73]

Because there also is the potential for benefit of intravenous GP IIb/IIIa inhibition prior to PCI,[74] it would appear

Table 10–6 Guideline Recommendations Regarding Intravenous GP IIb/IIIa Blockers in Patients with Non ST-Segment-Acute Coronary Syndrome

Patients who are being managed with an early invasive strategy (i.e., plan for early diagnostic catheterization)
- With aspirin and heparin—Class Ia, evidence level A*
- With aspirin, heparin, and clopidogrel—Class IIa, evidence level B

Patients with who are being managed with an early conservative strategy (i.e., no plans for diagnostic catheterization)
- If continuing ischemia, elevated troponin, or other high-risk features—Class IIa, evidence level A†
- If none of the above present—Class IIb, evidence level A†

*European guidelines[42] emphasize this recommendation among patients with an elevated troponin or diabetes.
†Eptifibatide or tirofiban only. Abciximab is Class III (evidence level A).
Modified from references 1 and 42.

reasonable to begin therapy early ("upstream"), although this has not been rigorously proved. This is the central hypothesis being tested in a large international study known as EARLY ACS that is comparing upstream eptifibatide with placebo before angiography in patients with high-risk NSTE-ACS who are managed with an early invasive strategy.[75]

Several additional unanswered questions with regard to intravenous GP IIb/IIIa blockers are being explored in ongoing studies. Can other oral antiplatelet, intravenous antiplatelet, and/or more efficacious anticoagulant drugs be as effective as intravenous GP IIb/IIIa blockers? Is there still a need for multiple antiplatelet agents? These are increasingly interesting issues particularly as more potent oral agents are developed.

Mechanistic studies support the addition of intravenous GP IIb/IIIa blockers to aspirin and thienopyridines because the latter two agents are not sufficient to achieve the high-grade platelet inhibition that is associated with a reduction in clinical events in PCI. Results from clinical studies, however, are conflicting, and only one large study has been completed in patients with NSTE-ACS. In the TOPSTAR trial,[76] addition of an intravenous GP IIb/IIIa blocker to aspirin and clopidogrel (including preloading with 375 mg the day before PCI) was associated with a reduction in the composite of death, MI, or urgent target vessel revascularization at 9 months. Similarly, in the CLEAR PLATELETS study,[77] fewer periprocedural MIs were present with intravenous GP IIb/IIIa blockade, even when 600 mg clopidogrel was administered 2 to 6 hours before PCI. Meanwhile, intravenous GP IIb/IIIa blockers did not improve outcomes in studies of stable low-risk patients[78] and in diabetics[79] who underwent PCI when 600 mg clopidogrel was used as background therapy. Intravenous GP IIb/IIIa blockade plus unfractionated heparin was not superior to bivalirudin in a third trial.[80] More recently, among 2022 patients with NSTE-ACS who were undergoing PCI all of whom were preloaded with 600 mg of clopidogrel at least 2 hours before PCI, the GP IIb/IIIa inhibitor abciximab reduced ischemic complications by 25% in the ISAR-REACT 2 trial.[81] The benefit was seen only in patients with a positive troponin at baseline. There was an excess of thrombocytopenia but no difference in clinically important bleeding among patients treated with abciximab.

Preliminary results of the ACUITY Timing Trial,[82] which compared early administration of GP IIb/IIIa inhibition with initiation in the catheterization laboratory as needed in 9207 patients with NSTE-ACS, were presented at the 2006 ACC Scientific Sessions. The primary endpoint (net clinical benefit including death, reinfarction, ischemia leading to unplanned revascularization, major bleeding) was 11.7% in both groups, meeting the prespecified statistical criterion for non-inferiority. However, delayed GP IIb/IIIa inhibition was associated with a numerically higher rate (7.9% versus 7.1%) of the ischemic complications (death, reinfarction, ischemia leading to unplanned revascularization) compared with upstream use, and did *not* fulfill the non-inferiority criterion. Major bleeding was reduced by approximately 20% with delayed use of GP IIb/IIIa. In patients who were undergoing PCI and in higher risk patients (troponin elevated at baseline, TIMI Risk Score 5 to 7), upstream GP IIb/IIIa inhibition appeared to offer some protection against ischemic complications. As additional detailed analyses are performed and published, further insight into the optimal use and timing of GP IIb/IIIa inhibitors may modify the current guideline recommendations (see Table 10–6).

Antiplatelet Drugs in Development

Well into clinical development are three antiplatelet agents that are more potent than the currently available oral antiplatelet drugs. Prasugrel is a thienopyridine that potentially offers three major advantages over clopidogrel: (1) faster onset of action[83] (owing to prehepatic metabolism along the path for generation of the active metabolite compared with exclusively intrahepatic metabolism for generation of the active form for clopidogrel); (2) higher degree of ex-vivo platelet inhibition; and (3) less intrapatient variability (i.e., fewer hyporesponders). In pharmacodynamic studies, prasugrel achieved a higher degree of ex-vivo platelet inhibition of ADP-induced platelet aggregation compared with standard dose clopidogrel,[84] and was as effective in patients who were hyporesponsive to clopidogrel as were those who achieved the expected pharmacodynamic response. In a phase 2 dose-ranging study of patients who were undergoing PCI (JUMBO-TIMI 26),[85] prasugrel (40 to 60 mg loading dose, maintenance 7.5 to 15 mg daily) was associated with similar bleeding rates and less frequent target vessel thrombosis and recurrent ischemia. Prasugrel (60 mg loading dose, 10 mg maintenance) is currently being compared with clopidogrel in a phase 3 trial of patients with ACS who are undergoing PCI (TRITON-TIMI 38).

AZD6140 is an oral antiplatelet agent that is the first member of a new class of $P2Y_{12}$ receptor antagonists known as the cyclopentyltriazolopyrimidines.[83] In phase 2 dose-ranging trials, AZD6140 (90 to 180 mg twice daily.) achieved higher levels of ADP-induced inhibition than clopidogrel, did not increase bleeding, and at a dose of 180 mg twice daily was associated with numerically fewer cardiovascular ischemic complications.[86]

Cangrelor is an intravenous ATP derivative that can achieve 90% inhibition of platelet aggregation (similar to intravenous GP IIb/IIIa blockers) and has a plasma half-life of 5 minutes, with recovery of platelet function 20 minutes after cessation of infusion.[87] In a phase 2 trial of patients who were undergoing PCI, cangrelor and abciximab were associated with similar low rates of post-PCI ischemic complications; whereas cangrelor was associated with one half the number of bleeding events.[88]

ANTICOAGULANTS

Beginning with the expression of tissue factor and ending with the production of thrombin, the biologic complexity of the coagulation cascade has yielded a number of promising targets for anticoagulation therapy (Fig. 10–5).[209] Agents that inhibit the earlier portion of the cascade (e.g., tissue factor [TF] antibodies, TF/VIIa complex inhibitors, factor Xa inhibitors) are potent inhibitors of thrombin generation, whereas those that target more distally (e.g., direct thrombin inhibitors [DTIs]) derive most of their pharmacologic effect by inhibiting preexisting thrombin. Because of biologic redundancies and multiple feedback loops in the coagulation system, inhibition at one level of the cascade can have complex effects that make it difficult to predict the clinical response to these drugs. UFH had been the standard anticoagulant for decades, although extensive study over the past 15 years with low-molecular-weight heparins (LMWHs), DTIs, and inhibitors of factor Xa, are leading to updates of practice guidelines (see Chapter 5).

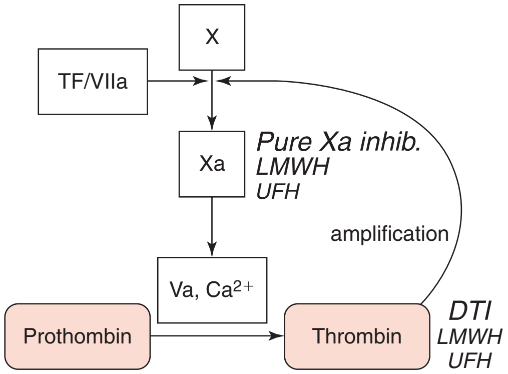


Figure 10–5 Activation of the coagulation cascade and platelet aggregation in patients with ACS. After disruption of a vulnerable plaque, tissue factor (TF) is exposed, complexes with factor VIIa, and initiates the coagulation cascade. Factor X is activated, and leads to the production of thrombin through its interaction with the prothrombinase complex (factor Va, factor Xa, calcium ion [Ca^{2+}]) on the membrane of activated platelets. Platelets may be activated via number of pathways—two of the more potent agonists are thrombin and adenosine 5′-diphosphate (ADP). The final common step to platelet activation is fibrinogen binding, which mediates platelet–platelet interaction. Unfractionated heparin (UFH) inhibits factor Xa and thrombin to a similar degree; whereas low-molecular-weight heparins (LMWHs) exert proportionally a greater effect on factor Xa, and direct thrombin inhibitors (DTIs) predominantly act only on thrombin. The larger font size indicates a qualitative greater effect at the position in the coagulation cascade shown. (Modified from Antman EM: The search for replacements for unfractionated heparin. Circulation 2001;103(18):2310-14.) (With permission).

Unfractionated Heparin and Low-Molecular-Weight Heparin

The optimal dose of unfractionated heparin (UFH) has not been rigorously established, however, several studies support a lower, weight-based dosing regimen[89] to improve the safety profile without apparent loss of efficacy (Table 10–7). UFH has a number of limitations (Table 10–8) that have led to the search for a replacement anticoagulant.

Unlike UFH, the LMWHs have a number of other advantages that include less nonspecific binding to proteins and platelets, less depletion of tissue factor pathway inhibitor, and greater inhibition of vWF. Furthermore, the better bioavailability and longer half-life permits subcutaneous dosing, thereby improving the ease of administration both in and out of hospital (see Table 10–8). Although more than a dozen different LMWH preparations have been developed, only two (enoxaparin and dalteparin) have been widely studied in patients with ACS.[90] Enoxaparin has a lower molecular weight (4200 versus 6000), slightly higher anti Xa:IIa ratio (3.8:1 versus 2.7:1), and greater inhibition of vWF compared with dalteparin. Both drugs are administered subcutaneously in a weight-based fashion in their maintenance dosing, whereas an intravenous bolus dose of 30 mg enoxaparin has also been studied in NSTE-ACS[91] and as an adjunct to fibrinolysis in STEMI (see Table 10–8). In the only randomized clinical trial that compared two LMWHs head-to-head, enoxaparin was more efficacious than tinzaparin.[92]

A meta-analysis of four trials composed of 999 patients demonstrated a large reduction (5.5% to 2.6%, $P = 0.018$) in death or MI with the addition of UFH to aspirin compared with aspirin monotherapy (see Chapter 1).[1] Similarly, the FRISC trial[93] demonstrated a 63% reduction in death or MI at 7 days with the LMWH dalteparin plus aspirin compared with aspirin monotherapy (4.8% versus 1.8%, $P = 0.001$). The current practice guidelines support adding a heparin preparation (either UFH or LMWH) to aspirin in patients with probable or definite NSTE-ACS.[1]

Eight randomized trials have compared LMWH with UFH on a background of aspirin.[1] Dalteparin and fraxiparin did not improve outcomes compared with UFH in the FRIC[94] and FRAXIS[95] trials, respectively. In two double-blind trials from the late 1990s (ESSENCE[14] and TIMI 11B[91]), enoxaparin was associated with an approximate 20% reduction in the triple composite that was statistically significant in each study. Two additional large-scale open-label clinical trials (A to Z,[96] SYNERGY[97]), in which patients were more likely to be managed with an early catheterization, compared enoxaparin with UFH and concluded that enoxaparin is not inferior to UFH, thus confirming enoxaparin as an effective alternative.

Peterson and colleagues[98] provided a systematic evaluation of the outcomes in 21,946 patients in six randomized controlled clinical trials that compared enoxaparin with UFH in patients with NSTE-ACS (Fig.10–6). There was a 9% significant reduction in the composite of death or nonfatal MI after 30 days with enoxaparin and no differences in major bleeding or blood transfusions. Patients who received an antithrombin before randomization appeared to experience higher absolute rates of bleeding. Thus, the practice of switching between antithrombins in the same patient in the course of a single hospitalization should be avoided whenever possible.

Given similar or slightly better efficacy with enoxaparin compared with UFH in patients and other practical conveniences (twice daily subcutaneous injections, absence of the need for routine monitoring, and simple weight-based dosing), the use of enoxaparin generally should be preferred over UFH in most patients with NSTE-ACS (class IIa recommendation).[1] For patients at increased risk of bleeding or for whom an early invasive strategy is planned, the benefits of enoxaparin should be weighed against the trend toward an increased risk of bleeding that was observed in some studies that compared enoxaparin with UFH.

Direct Thrombin Inhibitors

There are three parenteral direct thrombin inhibitors (DTIs)—hirudin, bivalirudin, and argatroban—currently available for clinical use in the United States.[99-101] They are termed “direct” because they do not require a cofactor, as do the heparins, and they directly inhibit existing thrombin while having minimal effects on the proximal portions of the coagulation cascade (see Fig. 10–5). DTIs can broadly be classified as either monovalent (e.g., argatroban, inogatran) or divalent (e.g., hirudin, bivalirudin).

A meta-analysis of five trials involving 20,570 patients with NSTE-ACS randomized to a DTI versus UFH concluded that DTI reduced death or MI by 20% (OR 0.80, 95% CI 0.70 to 0.92) from 4.6% to 3.7% with similar effects on death (OR 0.82) and MI (OR 0.78) individually.[102] DTIs were associated with a near doubling in the rate of major bleeding (1.0%

Table 10–7 Dosing of Antithrombotic Agents in Patients with Non ST-Segment Acute Coronary Syndrome

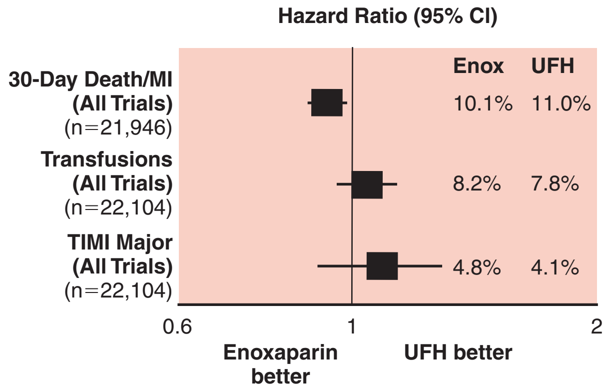
Anticoagulant	Loading Dose	Maintenance Dose*
Bivalirudin	0.1-0.25 mg/kg IV	0.125-0.5 mg/kg IV for ≥ 72 h
Dalteparin	None	120 IU† SC q12 h for ≥ 72 h
Fondaparinux	None	2.5 mg SC qd
Hirudin	0.1-0.4 mg/kg IV	0.1-0.15 mg/kg IV for 3-7 d 0.5 mg/kg SC bid for 3-7 d
Enoxaparin	30 mg IV ‡	1 mg/kg SC q12h§ for 2-8 d
Unfractionated heparin	60 U/kg¶ IV	12 U/kg/h‖ IV for ≥ 48 h

*Shortened administrations recommended if early catheterization/revascularization.
†10,000 IU maximum.
‡Studied in high-risk patients in TIMI 11b.
§q 24 hour dosing if creatinine clearance <30 mL/min.
¶4000 U maximum in patients with NSTE-ACS.
‖1000 U/h maximum initial infusion; thereafter titrated to a PTT 1.5-2.0 times control.
ACT target of 200-250 seconds (with glycoprotein IIb/IIIa inhibitors) or 250-300 seconds (without glycoprotein IIb/IIIa inhibitors) during PCI, discontinue at end of successful procedure if no other clinical indication for ongoing anticoagulation
PCI, percutaneous coronary intervention.

Table 10–8 Limitations of Unfractionated Heparin and Comparison with Other Anticoagulants

Properties of Unfractionated Heparin	Pharmacologic Consequences	Clinical Consequences	Comparator Anticoagulants: LMWH	DTI	FXa inhibitor
Thrombin-Dependent Properties					
Nonspecific protein binding	Less drug binding to thrombin	Variable anticoagulation levels; requires frequent monitoring	+	0	0
	Sensitivity to inactivation by PF4 and histidine-rich glycoprotein		+	0	0
Short plasma half-life	Poor bioavailability with single dose	IV infusion required	0	++	0
Depletion of TFPI	↓ Attenuation of TF/VIIa complex	Rebound hypercoaguability	0	++	0
Relative inability to inhibit fibrin-bound thrombin	Thrombin generation after clot lysis in presence of therapeutic levels	Rebound thrombosis during and post therapy	++	0	?
Requires cofactor (AT III) to optimally bind thrombin	↓ Thrombin-inhibition if AT III not available	Cannot be used in patients with AT III deficiency	0	0	++
Thrombin-Independent Properties					
↑ binding to platelets	Immunogenicity ↑ Platelet activation/ adhesion	↑ Potential for bleeding, HITTS, or thrombosis	+ +	0 0	0 0
Inability to blunt the increase in vWF levels	↑ vWF levels	↑ Potential for thrombosis	0	+	?
Primarily excreted renally	↓ Drug clearance, ↑ blood levels with renal insufficiency	↑ Potential for bleeding in renal insufficiency	++	*	++

*Dependent on the specific direct thrombin inhibitor.



A to Z did not include CABG data.

Figure 10–6 In a systematic overview[98] of six randomized clinical trials comparing enoxaparin with unfractionated heparin (UFH) in 21,946 patients with non ST-segment elevation-acute coronary syndrome (NSTE-ACS), enoxaparin was associated with a statistically significant reduction (0.9% absolute) in the rate of death or new myocardial infarction at 30 days. Rates of major bleeding and transfusion tended to be slightly higher with enoxaparin. TIMI, Thrombolysis in Myocardial Infarction (With permission).

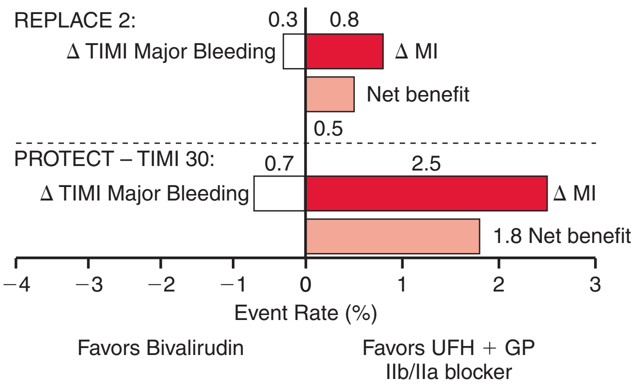


Figure 10–7 Comparison of bivalirudin (with provisional intravenous GP IIb/IIIa blocker) with unfractionated heparin (UFH) plus intravenous GP IIb/IIIa blocker with respect to the absolute difference in TIMI major bleeding, new myocardial infarction (MI) (mostly peri-PCI), and the net clinical benefit (difference in both endpoints combined) in REPLACE-2[80] and PROTECT-TIMI 30.[103] PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

versus 0.5%; OR 1.79, 95% CI 1.29 to 2.50), however, heterogeneity in the applied definitions and observed results (both between different agents and across studies with the same agent) limits the precision of this estimate. In addition, the reductions in ischemic events were inconsistent across different DTIs, with no evidence of benefit with monovalent agents (inogatran, effegatran). Thus, in patients with a history of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), hirudin (and perhaps bivalirudin, although data are limited) is a reasonable alternative to LMWHs and UFH.

Data are becoming available on the use of DTIs in patients who are treated with more modern adjuncts including the thienopyridines, intravenous GP IIb/IIIa inhibitors, and drug-eluting stents. In the REPLACE-2 trial[80] of 6010 patients who were undergoing urgent or elective PCI, bivalirudin (with provisional use of an intravenous GP IIb/IIIa blocker in 7% of patients) was not inferior to the combination of UFH and an intravenous GP IIb/IIIa blocker, as assessed by the quadruple composite endpoint of death, MI, urgent target vessel revascularization, and major bleeding. No differences emerged in long-term efficacy (death, MI, or repeat revascularization). Among 857 moderate- and high-risk patients with ACS who were undergoing PCI in the PROTECT-TIMI 30 trial,[103] bivalirudin was associated with a lower rate of normal myocardial perfusion, a longer duration of ischemia on ambulatory ECG monitoring among patients with ischemia, a trend toward a higher composite rate of death, MI, or ischemia, but no difference in coronary flow reserve. In both studies, transfusions and serious bleeding rates were significantly reduced with bivalirudin. There were, however, numerically more periprocedural infarctions (Fig. 10–7). In sum, the available results indicate that bivalirudin may be a safer and equally or perhaps slightly less effective alternative to the combination of heparin with an intravenous GP IIb/IIIa blocker.

Preliminary results from the ACUITY trial, which compared bivalirudin with or without GP IIb/IIIa inhibition with heparin plus glycoprotein IIb/IIa inhibition in 13, 819 patients with acute coronary syndromes,[104] were presented at the 2006 ACC Scientific Sessions.[82,105] Treatment with bivalirudin alone was associated with a reduction in the net clinical benefit (death, reinfarction, unplanned revascularization for ischemia, major bleeding) compared with UFH/enoxaparin plus GP IIb/IIIa, although the results were primarily driven by a reduction in bleeding. Additionally, bivalirudin alone was non-inferior (25% boundary) to UFH/enoxaparin plus GP IIb/IIIa inhibitor for the triple ischemic endpoint (death, reinfarction, unplanned revascularization for ischemia). Detailed publication of the final results should help guide clinicians regarding the relative usefulness of these various therapeutic combinations. Current practice guidelines consider DTIs to be first line anticoagulants in NSTE-ACS patients with a history of heparin-induced thrombocytopenia (with or without thrombotic syndrome),[1] and as an alternative to UFH plus intravenous GP IIb/IIIa blockers in low-risk elective PCI patients who are at risk for bleeding.[106]

Oral DTIs have also been developed[107] and could potentially have a role during or after NSTE-ACS. In a dose-ranging trial post-MI, ximelagatran was more effective than placebo at reducing ischemic complications, although an excess in asymptomatic elevation of liver function tests was noted with ximelagatran.[108] Furthermore, in larger studies to prevent venothromboembolism and to prevent embolic stroke in atrial fibrillation, rare but serious clinical hepatotoxicity was observed,[109] and an FDA advisory panel has recommended against its approval.

Factor Xa Inhibitors

Several parenteral[110] and oral[111] pure inhibitors of Factor Xa have been developed, and one synthetic parenteral pentasaccharide (fondaparinux)[112] is approved for use in the prevention and treatment of venothromboembolism. The OASIS-5

trial[113] compared fondaparinux 2.5 mg administered once daily subcutaneously with enoxaparin (1 mg/kg SC every 12 hours) in 20,078 patients with NSTE-ACS. Fondaparinux was not inferior to enoxaparin with respect to the primary efficacy triple composite of death, MI, or recurrent ischemia through 9 days (5.8% vs. 5.7%, HR 1.01 [0.90 to 1.13]). Fondaparinux was associated with approximately one half the number of major bleeding events (2.2% vs. 4.1%, HR = 0.52, $P < 0.001$) and one quarter fewer transfusions, although the dosing of enoxaparin, particularly around the time of coronary angiography and PCI (when UFH was added in addition to enoxaparin), may not have been optimal. The mortality rates at 30 days ($P = 0.02$) and 6 months ($P = 0.05$) were lower with fondaparinux. Ongoing studies are evaluating long-acting pentasaccharides (idraparinux, administered SC once weekly) and oral factor Xa inhibitors.

Other Anticoagulants

Drugs with proximal targets in the coagulation cascade, such as tissue factor (TF) antibodies, TF pathway inhibitors, and TF/fVIIa complex inhibitors, are in the early stages of clinical development.[114] Drugs that modulate the mid-portion of the cascade (inhibitors of Factor IX and the protein C pathway) are also being developed. Drugs that target TF or the TF/FVIIa complex block the initiation of the coagulation cascade and appear to be potent inhibitors of new thrombin generation. In contrast, inhibitors of the mid-portion of the cascade prevent thrombogenesis by attenuating the propagation of coagulation. Because of the complexity and biologic redundancy of the coagulation system, it is difficult to predict from ex vivo mechanistic studies, which, if any, of these strategies will be most useful in clinical practice, although clinical studies are ongoing with several of these compounds.

INVASIVE VERSUS CONSERVATIVE STRATEGY FOR CARDIAC CATHETERIZATION

In addition to the pharmacologic measures used to treat patients with UA/NSTEMI, one of the most important decisions during hospitalization is the early strategy of care regarding coronary angiography and resultant revascularization. The goals of coronary angiography are to provide information about prognosis based on location and extent of coronary atherosclerosis and to identify patients who will derive clinical benefit from revascularization (either percutaneous or surgical). An *early conservative* strategy refers to medical management of patients, reserving the use of coronary angiography and revascularization for evidence of recurrent ischemia at rest (or with minimal activity) or a strongly positive predischarge stress test. An *early invasive* strategy refers to the routine recommendation for coronary angiography and revascularization (within 12 to 48 hours of presentation) in patients without contraindications.

Several clinical trials have been performed to evaluate the question of which strategy is superior in the treatment of patients with UA/NSTEMI. Early trials such as TIMI III B[115] and VANQWISH[116] showed similar clinical outcomes regardless of treatment strategy. However, more contemporary trials that employed modern antiplatelet, antithrombotic and catheterization techniques, including FRISC II[117] and TACTICS-TIMI 18,[118] have shown a significant benefit from pursuing an early invasive strategy, especially in patients who have indicators of high risk.

To reconcile the differences in clinical trials of invasive versus conservative strategies, three meta-analyses were performed. Each of the three meta-analyses[119-121] demonstrated a benefit for an early invasive strategy compared with an early conservative strategy. A meta-analysis by Mehta and colleagues that included TIMI 3B, VANQWISH, FRISC II, TACTICS and others[119] concluded that a routine invasive strategy was associated with a significant reduction in death or MI, a nonsignificant trend toward fewer deaths, and a significant relative reduction in MI alone through the end of follow-up, with an early increase in events outweighed by a later reduction (Fig. 10–8). A meta-regression analysis[120] showed that the most significant predictors of the benefits of an early invasive strategy were the use of aggressive antiplatelet treatment (defined as use of an intravenous GP IIb/IIIa blocker or thienopyridine in addition to aspirin) and intracoronary stenting in the early invasive group, a conclusion supported by a direct comparison of two trials performed before (TIMI IIIB) and after (TACTICS-TIMI 18) these agents were routinely available.[122] These combinatorial analyses have strengthened the evidence for a routine invasive strategy.

One study stands in contrast to the data that favor an early invasive strategy. In the ICTUS trial of 1200 patients with NSTE-ACS, an elevated troponin T, and either ischemic electrocardiographic changes or a documented history of CAD, randomization to an early invasive versus a selective invasive strategy demonstrated similar rates of death, MI, or rehospitalization for ACS at 1 year.[123] Potential explanations for the lack of benefit with an early invasive approach include the high rate of catheterization and revascularization in the conservative arm and a relatively short-term follow-up period compared with other studies.[124]

In summary, the majority of data suggest a benefit for patients with NSTE-ACS who are treated with an early invasive strategy. This benefit appears to be particularly strong in patients with high-risk indicators (Table 10–9), with the strongest benefit for those patients with ST-segment deviation and elevated cardiac troponins. In the absence of these findings, an equal recommendation is given for either strategy in clinical practice guidelines.[1] It should be noted, however, that patients treated conservatively should be managed invasively if they develop high-risk indicators or have a strongly positive stress test before discharge. Once an invasive strategy is undertaken, the decision for revascularization is based on the results of the coronary angiography and is similar to the indications for revascularization in patients with chronic stable angina,[125] with a stronger indication for some form of revascularization owing to the severity of presenting symptoms.

HOSPITAL DISCHARGE AND POST-HOSPITAL CARE

After the initial stabilization of an episode of NSTE-ACS with medical therapy and/or revascularization, patients remain at increased risk for major cardiovascular events for 1 to 3 months, and then they revert to a risk profile that approximates the

Study	Routine No./Total (%)	Selective No./Total (%)
Randomization to Hospital Discharge		
TIMI 3B	51/740 (6.9)	45/733 (6.1)
VANQWISH	36/462 (7.8)	15/458 (3.3)
MATE	3/111 (2.7)	3/90 (3.3)
FRISC II	78/1222 (6.4)	38/1235 (3.1)
TACTICS	38/1114 (3.4)	49/1106 (4.4)
VINO	1/64 (1.6)	6/67 (9.0)
RITA 3	31/895 (3.5)	21/915 (2.3)
Subtotal	**238/4608 (5.2)**	**177/4604 (3.8)**
Hospital Discharge to Follow-up		
TIMI 3B	35/689 (5.1)	56/688 (8.1)
VANQWISH	116/426 (27.2)	124/443 (28.0)
MATE	13/108 (12.0)	8/90 (8.9)
FRISC II	49/1144 (4.3)	136/1197 (11.4)
TACTICS	43/1076 (4.0)	56/1057 (5.3)
VINO	3/63 (4.8)	9/61 (14.8)
RITA 3	64/864 (7.4)	97/894 (10.9)
Subtotal	**323/4370 (7.4)**	**486/4430 (11.0)**
Randomization to Follow-up		
TIMI 3B	86/740 (11.6)	101/733 (13.8)
VANQWISH	152/462 (32.9)	139/458 (30.3)
MATE	16/111 (14.4)	11/90 (12.2)
FRISC II	127/1222 (10.4)	174/1235 (14.1)
TACTICS	81/1114 (7.3)	105/1106 (9.5)
VINO	4/64 (6.3)	15/67 (22.4)
RITA 3	95/895 (10.6)	118/915 (12.9)
Subtotal	**561/4608 (12.2)**	**663/4604 (14.4)**

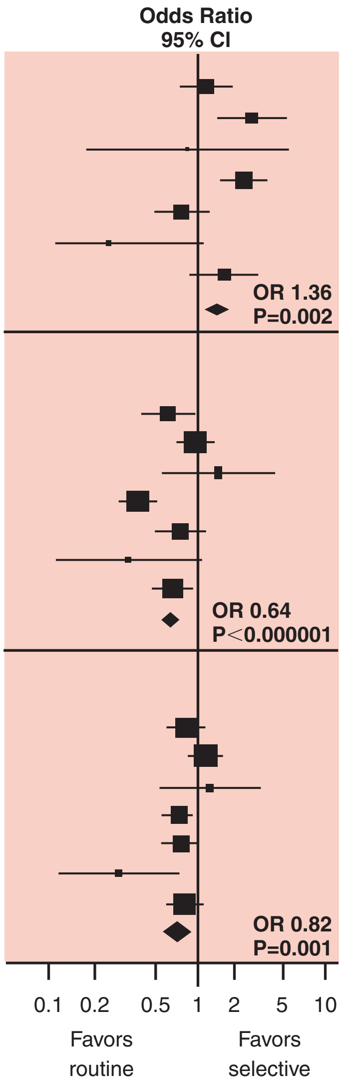


Figure 10–8 Composite of death or myocardial infarction (MI) in-hospital, post-discharge, and overall in trials of routine (early invasive) versus selective (early conservative) management of acute coronary syndrome (ACS).[119] Tests for heterogeneity: death or MI from randomization to hospital discharge, $P = 0.001$; death or MI after hospital discharge to follow-up, $P = 0.001$; death or MI from randomization to follow-up, $P = 0.06$. Random effects model results: death or MI from randomization to hospital discharge, relative risk (RR) 1.31, 95% CI 0.85 to 2.01; death or MI after hospital discharge to follow-up, RR 0.65, 95%CI 0.46 to 0.91; death or MI from randomization to follow-up, RR 0.82, 95%CI 0.68 to 0.99.

profile of patients with chronic stable CAD. Thus, institution of an effective comprehensive discharge plan is crucial to prevent early recurrent ischemic events. Critical pathways and various discharge tools are useful to increase adherence with treatment guidelines and have been associated with improved clinical outcomes.

Most patients can be discharged within 24 hours after a normal or low-risk noninvasive evaluation, or within 24 hours after uncomplicated PCI. Patients who are managed with CABG and have no major postoperative issues can generally be targeted for discharge to home or a short-stay rehabilitation facility on postoperative days 5 through 7. Three important goals in the discharge period include

1. Evaluation and patient education regarding NSTE-ACS, procedures performed, secondary risk factor reduction, and discharge medications, diet, and exercise.
2. Instructions regarding the appropriate level of activity and plans to resume usual activities in the near future.
3. Confirmation of long-term medical follow-up.

Table 10–9 High-Risk Indicators Favoring An Early Invasive Strategy for Patients with Unstable Angina/Non ST-Segment Elevation Myocardial Infarction[1]

- Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy
- Elevated cardiac troponin (I or T)
- New or presumably new ST-segment depression
- Recurrent angina/ischemia with CHF symptoms, an S3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
- High-risk findings on noninvasive stress testing
- Depressed left ventricular function (EF < 40%) on noninvasive testing
- Hemodynamic instability
- Sustained ventricular tachycardia
- Percutaneous coronary intervention (PCI) within 6 months
- Prior coronary artery bypass grafting (CABG)

CABG, coronary artery bypass graft; EF, ejection fraction; PCI, percutaneous coronary intervention.

A multidisciplinary approach that involves physicians and their assistants, nurses, pharmacists, dietitians, and rehabilitation specialists can help achieve these goals. Gluckman and associates[126] developed an "ABCDE" approach (Table 10–10) for the management of NSTE-ACS that provides a practical and systematic means to implement evidence-based medicine, including both medication (Table 10–11) and life-style modification (Table 10–12) into clinical practice.

Table 10–10 ABCDE Approach for the Management of Non ST-Segment Elevation Acute Coronary Syndrome

A: Antiplatelet therapy, **A**nticoagulation, **A**ngiotensin-converting enzyme inhibitor, **A**ngiotensin receptor blockade
Aspirin: ≥75 mg daily, continue indefinitely. Higher doses post-stenting.
Anticoagulation: atrial fibrillation, LV thrombus, severe wall-motion abnormalities
ACE-I: congestive heart failure, LVEF < 0.40, hypertension, diabetes. (May substitute ARB if intolerant of ACE-I).

B: β-blockade, **B**lood pressure control
β-blockade: all patients without absolute contraindications
Blood pressure control: goal < 130/85 mm Hg using lifestyle modifications and medications as needed.

C: Cholesterol treatment, **C**igarette smoking cessation
Cholesterol: Low saturated fat (<7% total calories), low cholesterol (<200 mg/day) diet rich in fish with omega-3 fatty acids (or supplemented by omega-3 supplements of 1 g/day). Goal LDL is <<100 mg/dL (optional target <70 mg/dL).
Cigarettes: ask, advise cessation, avoid second-hand exposure

D: Diabetes management, **D**iet
Diabetes: Goal glycosylated hemoglobin <7%, treat other risk factors
Diet: low in saturated fat and cholesterol, rich in omega-3 fatty fish, fresh vegetables, whole grains. Goal body mass index 18.5-24.9 kg/m^2. Routinely measure waist circumference, goal <40 inches (men), <35 inches (women).

E: Exercise: Ideally ≥30 minutes daily, supplemented by active lifestyle. Refer to cardiac rehabilitation/secondary prevention for patients with multiple risk factors or if supervised exercise program required due to high-risk status.

Adapted from Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non ST-Segment Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Available at: http://www.acc.org/clinical/guidelines/unstable/unstable/pdf.

Table 10–11 Discharge Medications for Patients with Non ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)

Aspirin (75 to 325 mg daily)
Clopidogrel (75 mg daily for patients intolerant to aspirin), or in addition to aspirin for a period of up to 9 months
β-Blocker in the absence of absolute contraindications
Lipid-lowering agent and diet in patients with LDL > 130, or LDL > 100 after diet therapy
ACE inhibitor (or ARB if intolerant of ACE-I) for patients with CHF, LV dysfunction (EF < 40%), hypertension, or diabetes mellitus
Sublingual or spray nitroglycerin with instructions on proper use

Adapted from Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non ST-Segment Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Available at: http://www.acc.org/clinical/guidelines/unstable/unstable/pdf.

Table 10–12 Lifestyle Modifications

Risk Factor	Goal/Target
Smoking cessation	Complete cessation, avoidance of secondary exposure
Weight control	BMI 18.5-24.9 kg/M^2 ; waist circumference <40 inches (men), <35 inches (women)
Exercise	Daily aerobic exercise for ≥30 minutes, minimum 3-4 times weekly*
Diet	≤7% calories from saturated fat, ≤200 mg/day cholesterol.
	↑ Fresh vegetables and fruit, fish rich in omega-3 fatty acids, whole grains, soluble fiber
Cholesterol management	LDL-C substantially <100 mg/dL, non-HDL substantially <130 mg/dL, TG < 200 mg/dL
Blood pressure control	<130/85 mm Hg (<130/80 if diabetes or chronic kidney disease), modest sodium restriction
Diabetes management	Glycosylated hemoglobin <7%
Depression/Anxiety	Assessment of psychosocial status, appropriate referral for support and/or therapy

*Optimally daily.
Adapted from Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non ST-Segment Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). Available at: http://www.acc.org/clinical/guidelines/unstable/unstable/pdf.

Antiplatelet Therapy, Anticoagulation, Angiotensin-Converting Enzyme Inhibitor, Angiotensin Receptor Blockade

All patients without an absolute contraindication should be discharged on aspirin to be continued indefinitely.[1,42] Oral anticoagulation therapy at discharge is recommended for patients who have atrial fibrillation or left ventricular (LV) thrombus, and is reasonable in patients with LV dysfunction and extensive regional wall-motion abnormalities.[1,42,127] More frequent monitoring of the patient is advised when combining warfarin with antiplatelet therapy. ACE-I is indicated in patients with congestive heart failure, LV ejection fraction <0.40, hypertension, or diabetes.[1,42] For patients intolerant of ACE-I, an angiotensin receptor blocker may be substituted.

β-Blockade, Blood Pressure Control

β-Blockers are recommended for all patients in the absence of absolute contraindications[1,42] (see Anti-ischemic Medications, earlier). The dose should be adjusted as needed to manage angina and blood pressure, with a target blood pressure of <130/80 mm Hg.

Cholesterol Treatment, Cigarette Smoking Cessation

The primary goal of cholesterol management in patients after ACS should be a target LDL-C substantially less than 100 mg/dL (with an optional target of <70 mg/dL).[128] Statins, initiated *before* discharge, are preferred as first-line agents to lower LDL-C in patients with an LDL-C <100 mg/dL, whereas statins in combination with other lipid-lowering drugs (e.g., ezetimibe 10 mg/day, bile acid sequestrants, or niacin) may be necessary in patients whose LDL-C is >100 mg/dL. An additional key goal is to reduce the non-HDL-C (total cholesterol minus HDL cholesterol) to substantially <130 mg/dL.[129] If the triglycerides are 200 to 499 mg/dL after initiating LDL-C–lowering therapy, then a fibrate or niacin may be added. For patients with higher triglycerides levels, fibrate or niacin should be considered before initiating LDL-C–lowering therapy.

In the PROVE-IT-TIMI 22 trial,[130] 4162 patients hospitalized with ACS were randomized within 10 days to either pravastatin 40 mg or atorvastatin 80 mg daily and followed for a mean of 24 months. Atorvastatin 80 mg reduced the median LDL-C further (62 mg/dL versus 95 mg/dL, $P < 0.001$), and patients experienced 16% deaths or major cardiovascular events over 2 years ($P = 0.005$). Interestingly, the reduction in clinical events became apparent quite early (within 30 days) after the initiation of therapy.[131] An important corollary observed in PROVE-IT-TIMI 22 was that acute anti-inflammatory effects were associated with better clinical outcomes. In a retrospective analysis, patients who achieved a CRP level <2 mg/L had lower event rates than those who had higher CRP levels regardless of the LDL-C achieved (Fig. 10–9).[210] Prospective confirmation of the relationship between the achievement of the dual goals and improved clinical outcomes is underway in ongoing studies.

In the Z phase of the A to Z trial,[132] 4487 post-ACS patients were randomized to an early initiation of intensive statin (simvastatin 40 mg/day for 1 month followed by 80 mg/day thereafter) or a delayed conservative statin regimen consisting of diet with placebo for 4 months followed by 20 mg/day thereafter for an average of 2 years. A favorable trend toward a lower rate of the primary composite endpoint of cardiovascular death, nonfatal MI, readmission for ACS, and stroke was observed with the early intensive statin arm (14.4% versus 16.7% for the delayed conservative arm, $P = 0.14$). Although no difference between these arms was evident during the first 4 months after randomization, between 4 months through the end of the study, the primary composite was reduced significantly by 25% in the high-dose simvastatin group ($P = 0.02$).

The available data now support the use of an intensive statin regimen, such as atorvastatin 80 mg/day in patients post ACS, preferably commencing during the index admission. Reducing CRP appears to be an equally important goal. The IMPROVE IT trial is comparing the combination pill simvastatin/ezetimibe with simvastatin monotherapy in 10,000 patients stabilized within 10 days after admission for ACS.

The letter *C* (for cigarettes) in the *ABCDE* mnemonic also reminds the health care provider to ask the patient about his

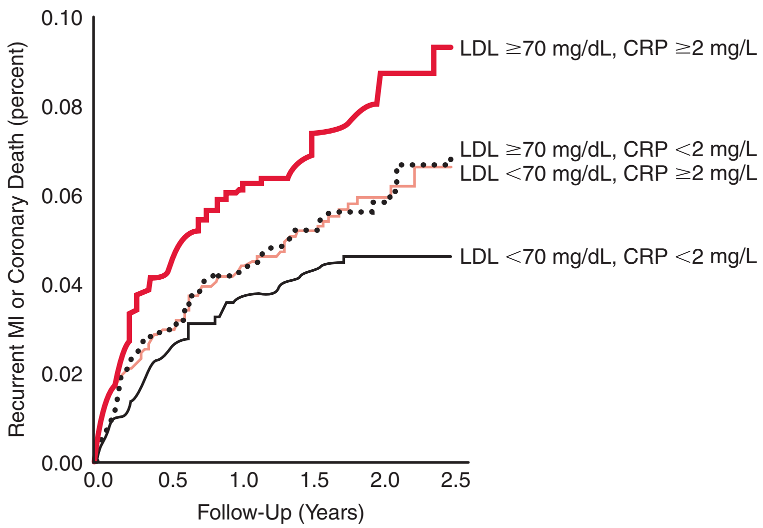


Figure 10–9 An analysis from the PROVE IT-TIMI 22 trial[210] of achieved LDL and achieved hs-CRP, stratified at cut points of 70 mg/dL and 2 mg/L, respectively, identified four groups of patients. Event rates were highest in the group with "high" LDL and "high" hs-CRP, and lowest in the group with "low" LDL and "low hs-CRP." PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infectious Therapy—Thrombolysis in Myocardial Infarction 22; LDL, low-density lipoprotein; CRP, C-reactive protein. (With permission).

or her tobacco status. Patients and family members should be strongly encouraged to stop smoking, and avoidance of exposure to environmental tobacco smoke at work and home should be urged.[1] Practical measures that can be taken by all physicians include assessment of the patient's willingness to quit, counseling and developing a plan for quitting, considering pharmacologic therapy (e.g., nicotine replacement, buproprion), and referral to specialized programs.

Diabetes Management, Diet

The goal of diabetes management is a glycosylated hemoglobin <7%. A diet limiting saturated fats and dietary cholesterol, while rich in omega-3 fatty fish, vegetables, and whole grains, is recommended to achieve a goal body mass index of 18.5 to 24.9 kg/m^2 (weight in kg/height in meters squared).[1] The waist circumference should be measured as part of the evaluation, and increased values (>40 inches in men, >35 inches in women) should trigger lifestyle changes and consideration of treatment strategies for the metabolic syndrome.

Exercise

All patients ideally should exercise for a minimum of 30 minutes, preferably daily, but at a minimum of 3 to 4 days per week, supplemented by an increase in daily lifestyle activities such as walking during work breaks, gardening, and household work.[133] Referral to cardiac rehabilitation or secondary prevention programs is recommended for patients with multiple modifiable risk factors and for those patients at higher risk for whom a supervised exercise training program is indicated.

SPECIAL CONSIDERATIONS

Cardiac Syndrome X

The term "cardiac syndrome X," or more simply "syndrome X," was introduced in 1973 by Kemp in an editorial[134] commenting on a study that investigated ECG and hemodynamic responses to atrial pacing in patients with chest pain and normal coronary angiograms.[135] One interesting subgroup of patients, labeled group X, had normal LV performance function despite typical ischemic ECG changes and increased myocardial lactate production consistent with myocardial ischemia. The three characteristic features of this clinical entity include: (1) anginal discomfort with exertion, (2) ST-segment depression on exercise treadmill testing, and (3) normal coronary angiography (including no evidence of spontaneous or inducible spasm).[136,137] Although there is a lack of consensus regarding the specific definition of cardiac syndrome X (e.g., some definitions do not require the presence of ischemic ECG changes during exercise), and the pathogenic mechanisms responsible for this condition appear to be multiple, we include cardiac syndrome X in this chapter because up to 15% of patients with ACS do not have hemodynamically significant evidence of CAD by conventional angiography.[138] Importantly, cardiac syndrome X must not be confused with "metabolic syndrome X" (which is defined as patients who have at least three of the following five criteria: increased waist circumference, elevated triglycerides, high blood pressure, elevated fasting glucose, or depressed HDL)[139] although a small number of patients may have both conditions.

The two major pathogenic mechanisms that are believed to be responsible for cardiac syndrome X are coronary microvascular dysfunction[140] and abnormal cardiac pain sensitivity (either or both may be present in any one individual).[141] The presence of microvascular dysfunction is supported by studies that have demonstrated impairment of endothelial-dependent arterial vasodilatation—including coronary artery hyperreactivity and spasm in some patients; abnormal levels of metabolic/hormonal mediators of vascular tone (decreased nitric oxide production, estrogen deficiency, release of the endogenous peptides neuropeptide Y, endothelin-1); increased sensitivity to sympathetic stimulation with increased sympathetic tone; and prearteriolar constriction, and/or coronary vasoconstriction in response to exercise that may be due, in part, to increased platelet aggregability.[142,143] The observations that CRP levels are elevated in cardiac syndrome X[144] and that CRP has been related to endothelial dysfunction[145] are more evidence of the importance of coronary microvascular dysfunction as a potential mechanism.

Abnormal cardiac pain sensitivity is a nonischemic mechanism that also appears to be operative in a substantial proportion of patients with cardiac syndrome X. Studies have demonstrated enhanced pain perception,[146] exaggerated pain response to adenosine, abnormal release of interstitial potassium, and activation of the right anterior insula cortex that may result in abnormal neural function.[147] It has also been postulated that both microvascular dysfunction and abnormal pain perception are operative as independent abnormalities, and that in some patients, the cardiac syndrome X becomes manifest only because of the presence of coronary microvascular dysfunction in patients with increased cardiac pain perception.[143]

Reassurance regarding the overall excellent prognosis remains the first step in management of patients with cardiac syndrome X. Treatments to prevent angina generally fall into one of four major categories: anti-ischemics, agents that improve endothelial function, analgesics, and lifestyle/behavioral approaches.[148] The most extensive data support the use of β-blockers as first-line therapy, with studies demonstrating a reduction in chest pain, less exercise-induced ST-segment depression, fewer episodes of silent ischemia by Holter monitoring, improvement in microcirculation, and better quality of life. Data from clinical trials have also (inconsistently) supported a role for nitrates and calcium channel blockers, particularly to reduce exercise-induced angina and ischemic ST changes. Nicorandil[149] (an adenosine triphosphate sensitive potassium channel opener that also has nitrate-like effects) and trimetazidine[150] (an inhibitor of oxidative phosphorylation that shifts energy production from free fatty acid to glucose oxidation) have also been associated with improvements in exercise tolerance, whereas α-blockers and aminophylline appear to have a more limited role in selected patients.

Because impairment in normal endothelial function of the coronary microvasculature that results in inadequate flow reserve appears to play an important role in some patients with cardiac syndrome X, therapies aiming to improve endothelial function have been tried with modest success. In a placebo-controlled trial, pravastatin 40 mg/day improved brachial artery flow-mediated dilatation, exercise duration, and time to ischemia in patients with cardiac syndrome X.[151] A study combining ACE-inhibition with statin therapy sug-

gested that these agents can improve endothelial function and quality of life in cardiac syndrome X and may work by reducing oxidative stress (as determined by superoxide dismutase activity) in the vascular wall.[152] Estrogen therapy, while improving endothelium-dependent coronary vasomotion in some postmenopausal women with cardiac syndrome X, is controversial, particularly in light of randomized trials of hormonal replacement that demonstrate an increase risk of cardiovascular events.[153]

When anti-ischemic drugs and statins prove ineffective at controlling symptoms, a trial of analgesic-based therapies is recommended, given the evidence of altered somatic and visceral pain perception in some patients with cardiac syndrome X. Imipramine reduced chest pain in placebo-controlled trials, including studies with[154] and without[155] concomitant background anti-ischemic therapy. Monitoring of side effects (e.g., dizziness, dry mouth, constipation) is necessary because these can have an adverse impact on quality of life.[154] Electrostimulation techniques such as transcutaneous electrical nerve stimulation[156] and spinal cord stimulation[157] reduced symptoms in studies of patients with angina and normal coronary angiograms, and thus may be considered for patients with angina refractory to multiple drug therapies. Physical training improves exercise capacity and delays the onset of exercise-induced angina, particularly among patients who are deconditioned.[158] Structured cognitive behavioral approaches, particularly if instituted early after diagnosis, may be helpful to reduce chest pain and the psychological morbidity associated with cardiac syndrome X.[159-162]

Because there is heterogeneity among patients diagnosed with cardiac syndrome X, an individualized patient-based approach that attempts to achieve optimal symptom control, using multiple disciplines if necessary, is recommended. Reassurance regarding the excellent intermediate-term prognosis along with a sympathetic appreciation by the physician of the adverse impact on quality of life that patients often experience are keys to success. A stepwise and largely empiric approach is described in Figure 10–10, pending additional data from randomized studies.

Cocaine Use and Acute Coronary Syndromes

Cocaine use results in a marked increase in sympathetic tone by blocking the reuptake of norepinephrine from synapses by preganglionic neurons. The use of cocaine favors myocardial ischemia and infarction through several mechanisms including increases in myocardial oxygen demand, decreases in myocardial oxygen supply, and accelerated atherosclerosis and thrombosis.[163] Oxygen demand is increased by increases in heart rate, myocardial contractility, and wall stress (β-adrenergic effects); supply is limited by vasoconstriction (α-adrenergic effects). However, the cardiovascular toxicity is not limited to dynamic effects. Cocaine also produces endothelial damage, enhanced platelet activation and aggregation, and decreases in plasminogen activator inhibitor.[163] Although the risk of events is highest when concentrations of cocaine in the blood are maximal and heart rate and blood pressure effects are apparent, these alternate pathophysiologic mechanisms may help to explain why patients using cocaine continue to be at risk for increased cardiac ischemic events after cocaine levels have decreased.

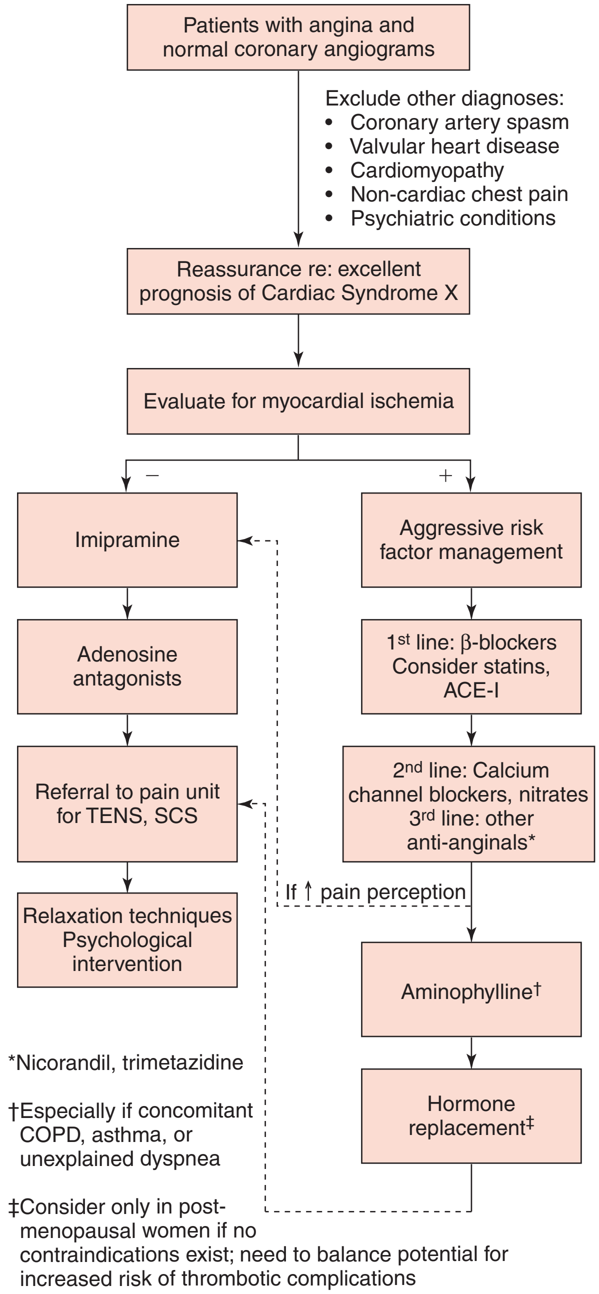


Figure 10–10 A stepwise approach to the diagnosis and management of patients with syndrome X.

The common use of cocaine among patients who present to emergency departments with chest pain and the differences in treatment between cocaine-induced coronary ischemia and patients without cocaine use mandate that the health care provider be vigilant to the possibility of use among all patients. Use of selective β-adrenergic receptor blockers can exacerbate coronary vasoconstriction in users of cocaine by creating a relative excess of β-adrenergic stimulation. Therefore, the use of selective β-blockers (as opposed to mixed α- and-β-blockers) as first-line agents for cocaine-related myocardial ischemia is discouraged.[163] Cocaine-related vasospasm can be reversed by verapamil, nitroglycerin, and α-adrenergic blockers such as phentolamine. Nitrates and calcium channel blockers and benzodiazepines are generally

considered first-line treatment for cocaine-related ischemia.[1] The clinician should remember, however, that coronary thrombosis is not infrequent with cocaine use, and aspirin and other antithrombotic measures should be taken. In the presence of refractory ischemia, cardiac catheterization with percutaneous intervention may be necessary.[1]

Women

Although CHD has traditionally been considered a disease of middle-aged men, approximately 43% of patients discharged with ACS from U.S. hospitals in 2003 were female.[5] In general, women diagnosed with NSTE-ACS should be managed in a manner similar to men, despite an under-representation of women in published trial literature that serves as the primary evidence for treatment guidelines. A number of key observations that pertain to women (on average) should be kept in mind. Women with NSTE-ACS tend to be older than men, with an incidence of CHD that lags by approximately one decade until the seventh decade.[164] The "typical" presentation of ACS that is based on earlier studies predominantly in men, differs from the "typical" presentation in women that is more complex and multifactorial.[165] Nonatherosclerotic etiologies of angina (e.g., microvascular dysfunction[166]) are more frequent in women than in men. Differences in the distribution and synergy of traditional and novel risk factors (e.g., CRP,[167] anemia[168]) between the sexes may explain the unique high-risk profile of certain subgroups of women with a protracted dysmetabolic state,[169] such as prematurely menopausal women who also have diabetes[170] or who smoke.[171] Gender-specific differences in pathophysiologic processes, possibly mediated by reproductive hormones (e.g., estrogen deficiency) may be responsible for the observed differences in biomarker profiles (lower troponin, higher BNP).[172]

Evaluation of women with biomarkers, ECG, noninvasive testing, and coronary angiography should be similar to an evaluation in men, although a few points deserve to be highlighted. Repolarization abnormalities on resting ECG are strong independent predictors of CHD events, mortality, and CHF in postmenopausal women.[173,174] Exercise ECG testing is less specific in women, and addition of an imaging study to the stress ECG improves diagnostic accuracy.[175,176] Because women have a more complex, multifactorial etiology of NSTE-ACS and greater diagnostic uncertainty, assessment of additional information (such as evaluation of plaque burden, vascular reactivity,[177] and functional capacity[178]) may be of relatively greater importance in women.[165] Similar to men, women with a high-risk indicator or with high-risk noninvasive test results should be referred for coronary angiogram with the understanding that women are at higher risk for bleeding complications, in part due to older age, lower body weight, and impaired renal function.

The reasons that women tend to be treated less intensively than men are likely complex and multifactorial.[179] Nonetheless, the underuse of proven therapies in NSTE-ACS that have a high benefit:risk ratio (e.g., aspirin, statin) indicates the presence of a gender treatment bias[180] that persists despite publication of numerous treatment guidelines over the past decade.[181] Women with CAD are referred less frequently for coronary angiography and revascularization,[181] in part due to the presence of less extensive epicardial CAD. The observation that women continue to have modestly poorer adjusted outcomes (particularly in the incidence of recurrent angina and CHF)[182] after revascularization, despite less extensive epicardial disease, suggests that we lack an adequate understanding of the relations between the gender differences in symptoms, risk factors, and pathophysiology.[183] Targeting obesity and physical inactivity may be especially important after NSTE-ACS as these factors contribute independently to CHD morbidity and mortality rates in women.[184]

Diabetes Mellitus

The prevalence of diabetes increased by 61% in the United States from 1990 to 2000, with some states experiencing rates of diagnosed diabetes in excess of 10%.[5] Because heart disease death rates among adults with diabetes are two- to fourfold higher than in adults without diabetes, and because nearly two thirds of all diabetics die of some form of heart or blood vessel disease,[185] diabetic patients with NSTE-ACS deserve particular attention.

In the Global Registry of Acute Coronary Events, more than one fourth of patients with NSTE-ACS had diabetes.[186] Diabetics tend to have a greater number of comorbidities, such as advanced age, prior CAD, history of heart failure, hypertension, and obesity—although they are less likely to smoke. Nevertheless, after multivariate adjustment, diabetes itself confers a 20% to 30% increased risk of death or ischemic complications.[187]

Established medical therapies for NSTE-ACS should be administered to diabetics as they are to nondiabetics, with additional attention directed toward tight control of blood glucose. Diabetics have a worse long-term outcome after revascularization compared with nondiabetics, in particular after PCI,[188] because they are at a higher risk for restenosis and disease progression of nonculprit lesions. Use of GP IIb/IIIa inhibitors and intracoronary stents appears to be of particular benefit in diabetics who undergo PCI.[189] With use of the left internal mammary artery as a bypass conduit, CABG is preferred over PCI in diabetics with multivessel disease,[190] although additional studies are needed with newer therapies (e.g., drug-eluting stents, thienopyridines) to determine the optimal role for multivessel PCI in diabetics.

The Elderly

Prevalent coronary artery disease increases with aging. As a result, elderly patients are over-represented among patients with coronary disease. It is reported that 20% of the hospitalizations for MI and, because adverse outcomes are more prevalent in the elderly, 30% of MI deaths are seen in the 5% of the U.S. population in their 80s.[191] Despite the burden of risk in elderly patients, evidence-based therapies are underused in this age group.[192-194]

More frequent medical and cardiac comorbidities affect all aspects of the diagnosis and management of elderly patients with NSTE-ACS. Risk factors and physiologic differences also are manifest in the care of older patients with NSTE-ACS. In the TIMI III registry, elderly patients were more likely to have systemic hypertension and a history of myocardial infarction, but less likely to have hypercholesterolemia, family history of coronary artery disease, or to smoke than the non-elderly.[194] Elderly patients are more likely than younger patients to have noncoronary causes of NSTE-ACS: hyperten-

sion, myocardial hypertrophy, and diastolic dysfunctions.[195] In addition, reduced hepatic and renal function results in impaired metabolism and clearance of medication. Elderly patients tend to have decreased arterial compliance that results in increased cardiac afterload and diminished β-sympathetic response.[196] These factors, combined with polypharmacy, increase the risk of drug–drug interactions and side effects in the elderly.

Elderly patients are more likely to present with atypical symptoms of UA/NSTEMI such as shortness of breath or congestive heart failure resulting from exaggerated increases in ventricular pressures.[197] Therefore, a high index of suspicion must be maintained for diagnosis of UA/NSTEMI in the elderly.

General recommendations for the pharmacologic treatment of UA/NSTEMI in the elderly is to follow the accepted treatment for younger patients, recognizing and anticipating increased side effect profiles of therapeutics in this population.[198] However, greater caution regarding dosing and monitoring of side effects is necessary. For instance, older patients are more prone to exaggerated hypotensive effects of nitroglycerin.[199] Elderly patients have diminished responsiveness to adrenergic stimuli and decreased atrioventricular (AV) nodal conduction, thus the response to β-blockers may not be predictable. Of particular importance, the prevalence of reduced renal function in the elderly is high, even in the setting of seemingly normal serum creatinine. Specific calculation of creatinine clearance or glomerular filtration rate should be performed in the elderly to guide therapy and dose medications that are cleared by the kidney.

Decisions regarding invasive or conservative management must also be considered in the context of the age of the patient. Elderly patients are more likely to have severe coronary artery disease which could benefit from invasive management, but also are more likely to have medical comorbidities that can result in adverse outcomes. Observational studies have shown that elderly patients are much less likely than younger patients to undergo coronary angiography and revascularization.[194,200] Studies have shown results similar to younger patients in carefully chosen subjects[201]; however, some studies show decreased procedural success rates and increased complications at extremes of age[202,203] including an increase in periprocedural MI.[204]

Most clinical trials have not specifically addressed the issue of invasive versus conservative management of the elderly. One prospective randomized trial (the TIME trial) of invasive versus conservative therapy in patients older than 75 years with *chronic* coronary artery disease has been published.[205] Patients who were undergoing revascularization had a lower rate of major adverse cardiac events at 6 months and improvement in symptomatic status compared with patients with an initial conservative management strategy. In an analysis of the TACTICS-TIMI 18 trial,[206] a larger clinical benefit was seen in elderly patients who were undergoing an invasive strategy than in younger patients, but was somewhat offset by an increased rate of hemorrhage in elderly patients. A similar pattern of risk and benefit was observed in the FRISC II trial, with the majority of the benefit of early invasive therapy being seen in patients older than 65 years.[117]

As with other treatments, the rates of important adverse events, including cerebrovascular events, after CABG is significantly increased in elderly patients.[207] Observational studies showed, however, improved clinical outcomes among octogenarians who underwent CABG compared with patients with similarly severe CAD who did not undergo CABG.[208]

An approach to the care of an elderly patient with NSTE-ACS should focus on factors similar to the management of younger patients. Because of physiologic and psychosocial differences, and because of more frequent polypharmacy and medical comorbidities, each therapy should be considered specifically for its possible adverse effects and interactions. The practitioner should attempt to identify the signs and symptoms of depression in the elderly and provide treatment.[191] Additionally, the importance of physical therapy and rehabilitation to maintain mobility and enhance recovery is magnified in the elderly.[191] **In summary, data suggest that well chosen elderly patients are likely to derive an important benefit from proven strategies. Barring medical comorbidities that provide contraindications, advanced age should be considered an indication for comprehensive treatment of NSTE-ACS, not a contraindication to it.**

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ST-Elevation Myocardial Infarction

Eric R. Bates and Frederick G. Kushner

CHAPTER CONTENTS

ST-elevation myocardial infarction (STEMI) is a significant health problem in industrialized countries and is becoming an increasingly significant problem in developing countries.[1] There are approximately 500,000 STEMI events in the United States each year.[2] One third of patients will die within the first 24 hours of presentation, many with sudden death.[1] In the last few decades, there has been a steady decline in the mortality rate from STEMI, but the rate of decline appears to have slowed. This appears to be due to both a fall in the incidence of STEMI and a reduction in the case fatality rate.[3] There has been a progressive increase in the proportion of patients who present with non-ST segment elevation myocardial infarction compared with STEMI. This chapter will follow the clinical course of the STEMI patient from before STEMI to management in the prehospital setting, the Emergency Department, the hospital, and after hospital discharge.[2]

PRE-STEMI MANAGEMENT

Primary and secondary prevention interventions aimed at the risk factors associated with coronary heart disease (CHD) reduce the risk of STEMI.[4,5] These include smoking cessation,[6] diet, exercise, lipid management,[7] blood pressure control,[8] and diabetes management (see Chapter 9). Primary care providers should evaluate the presence and status of control of major risk factors for CHD for all patients every 3 to 5 years. The 10-year risk of developing symptomatic CHD should be calculated for all patients who have two or more major risk factors to assess the need for primary prevention strategies.[4,7,9] Patients with established CHD should be identified for secondary prevention, and patients with a CHD risk equivalent (e.g., diabetes mellitus, chronic kidney disease, peripheral vascular disease, or a 10-year risk >20% as calculated by the Framingham equations) should receive equally intensive risk factor intervention as those with clinically apparent CHD.[10]

Morbidity and mortality due to STEMI can be reduced if patients and bystanders are taught to recognize symptoms early and activate the Emergency Medical Services (EMS) system.[11] Patients with symptoms of STEMI should be transported to the hospital by ambulance, instead of by automobile, so that they can receive cardiopulmonary resuscitation (CPR) and defibrillation, if necessary, and they should receive early reperfusion therapy at the nearest appropriate hospital.

Although the traditional recommendation is for patients to take one sublingual nitroglycerin dose 5 minutes apart for up to three doses before calling EMS, this recommendation has been modified to encourage earlier contact by STEMI patients.[12] If symptoms suggestive of STEMI are unimproved or worsening 5 minutes after one nitroglycerin tablet, patients should immediately call 911 to access EMS.

PREHOSPITAL MANAGEMENT

Symptom Recognition

Early recognition of symptoms of STEMI is the first step in the "Chain of Survival."[13] Although most patients recognize chest pain as a symptom of STEMI, many are unaware of associated symptoms, such as arm pain, lower jaw pain, shortness of breath, and diaphoresis or anginal equivalents.[14] For a variety of reasons the average patient does not seek medical attention for at least 2 hours after symptom onset.[15] Longer delay times occur among non-Hispanic blacks, older patients, Medicaid patients, and women.[16,17] Fully one third of patients with confirmed STEMI may present to the hospital with symptoms other than chest discomfort[18] and as many as one half of all STEMI events are clinically silent or unrecognized by the patient.[19] A high index of suspicion for STEMI should be maintained when evaluating women, diabetics, older patients, and those with a history of heart failure, as well as those patients complaining of chest discomfort but who have a permanent pacemaker or bundle branch block that may confound the recognition of STEMI on their electrocardiogram (ECG).

Out-of-Hospital Arrest

The majority of deaths from STEMI occur in the first 1 to 2 hours after symptom onset, usually from ventricular fibrillation (VF). Every minute in VF decreases the chance of survival by 7% to 10%.[13] Key elements of the "Chain of Survival" include early activation of the EMS system, early CPR and defibrillation for those who need it, and advanced cardiac life support (ACLS).[13,20] Family members of STEMI patients should be advised to take CPR and automated external defibrillator (AED) training.

Emergency Medical Services Systems

To minimize time to treatment, particularly for cardiopulmonary arrest, many communities allow volunteers and/or paid firefighters and other first-aid providers to function as first responders, providing CPR and early defibrillation using an AED until emergency medical technicians (EMTs) and paramedics arrive. The EMS ambulance response is a tiered system. The basic EMT level includes first aid and early defibrillation with AEDs. Other units are staffed by paramedics or other intermediate level EMTs who can give basic care, start IVs, intubate, and administer medications. In some systems, the advanced providers can also perform a 12-lead ECG, provide external pacing for symptomatic bradycardia, and employ other techniques.[21] Some high performance EMS systems have only advanced life support-staffed ambulances.

Prehospital EMS providers should administer 162 to 325 mg of chewable aspirin, unless contraindicated, to patients suspected to be experiencing STEMI. The use of 12-lead ECGs by paramedics to evaluate all patients with possible ischemic chest discomfort in the prehospital setting is strongly encouraged. For patients with ECG evidence for STEMI, a reperfusion checklist may be relayed along with the ECG to a predetermined medical control facility or hospital.

Prehospital Fibrinolysis

Randomized controlled trials have demonstrated the benefit of initiating fibrinolytic therapy as early as possible after the onset of STEMI.[22,23] Prehospital administration allows one half of patients to be treated within 2 hours of symptom onset when the greatest treatment benefit can be expected.[24] A French national registry demonstrated lower 1-year mortality with prehospital fibrinolytic therapy than with in-hospital fibrinolysis or primary PCI[25] (Fig. 11–1). However, a prehospital fibrinolytic program requires either a physician in the ambulance or a highly organized program with well-trained paramedics that can transmit the ECG to a medical command center with a medical director.

Prehospital Destination Protocols

Every community should have a written protocol that guides EMS system personnel in determining where to take patients with suspected or confirmed STEMI (Fig. 11–2). In general, patients with suspected STEMI should be taken to the nearest appropriate hospital. However, patients with contraindications to lytic therapy or patients with severe heart failure or cardiogenic shock should be transported directly or secondarily transported to a hospital with revascularization capability so that they can receive revascularization therapy. Hospitals without revascularization capability should also have an interhospital transfer protocol in place for patients who fail fibrinolytic therapy and are candidates for rescue PCI.

EMERGENCY DEPARTMENT MANAGEMENT

Patient Triage

The effectiveness of a variety of treatment options diminishes rapidly within the first several hours following symptom onset, so rapid triage is important.[26,27] The traditional Emergency Department (ED) evaluation of patients with chest pain relies heavily on the patient's history, physical examination, and ECG. All patients presenting to the ED with chest discomfort or other symptoms suggestive of STEMI should be placed on a cardiac monitor immediately with emergency resuscitation equipment nearby, including a defibrillator. An intravenous line should be started for rapid delivery of medications. An ECG should be performed and shown to an experienced Emergency Medicine physician within 10 minutes of ED arrival. Advanced directives should be clarified, especially in elderly patients, to prevent treatment contrary to the patient's wishes. If STEMI is present, the decision as to whether the patient will be treated with fibrinolytic therapy or primary PCI should be made within the next 10 minutes. The goal should be to achieve a door-to-needle time within 30 minutes or a door-to-balloon time within 90 minutes. If the initial

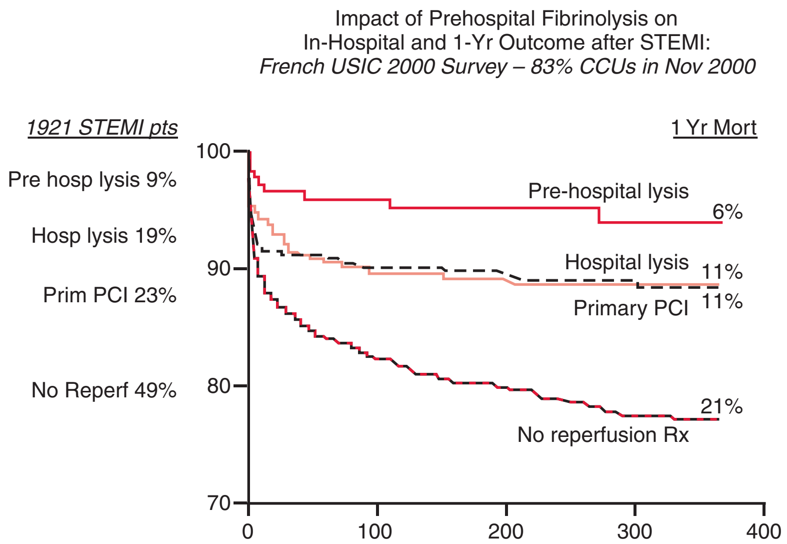


Figure 11–1 Age-adjusted Kaplan-Meier 1-year survival according to reperfusion strategy in the French USIC 2000 survey of 83% of coronary care units in November 2000. After adjustment by Cox multivariable analysis, prehospital thrombolysis remained associated with improved survival. CCUs, coronary care units; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. (Reproduced from Danchin N, Blanchard D, Steg PG, et al: Impact of prehospital thrombolysis for acute myocardial infarction on 1-year outcome: Results from the French Nationwide USIC 2000 Registry. Circulation 2004;110:1909-15).

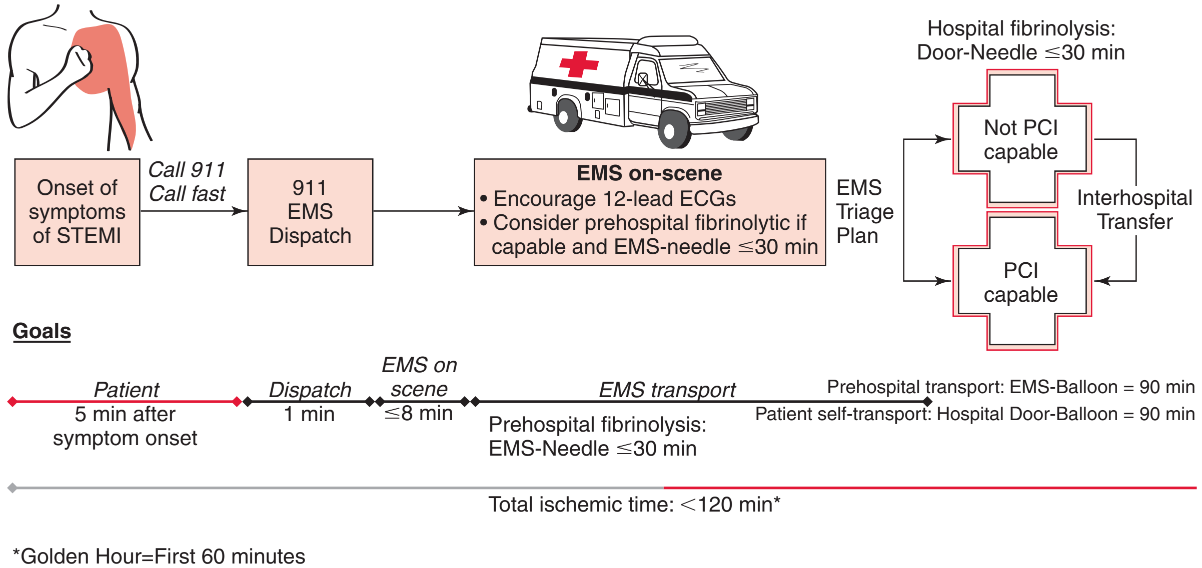


Figure 11–2 Options for transportation of patients with STEMI and initial reperfusion treatment. Patient transported by EMS after calling 911: Reperfusion in patients with STEMI can be accomplished by the pharmacologic (fibrinolysis) or catheter-based (primary PCI) approaches. Implementation of these strategies varies based on the mode of transportation of the patient and capabilities at the receiving hospital. Transport time to the hospital is variable from case to case, but the goal is to keep total ischemic time within 120 minutes. There are three possibilities (1) if EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis should be started within 30 minutes of EMS arrival on scene; (2) if EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a non–PCI-capable hospital, the hospital door-to-needle time should be within 30 minutes for patients in whom fibrinolysis is indicated; (3) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a PCI-capable hospital, the hospital door-to-balloon time should be within 90 minutes. Interhospital transfer: It is also appropriate to consider emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization if (1) there is a contraindication to fibrinolysis; (2) PCI can be initiated promptly (within 90 minutes after the patient presented to the initial receiving hospital or within 60 minutes compared with when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital; (3) fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI"). Secondary non-emergency interhospital transfer can be considered for recurrent ischemia. Patient self-transport: Patient self-transportation is discouraged. If the patient arrives at a non–PCI-capable hospital, the door-to-needle time should be within 30 minutes. If the patient arrives at a PCI-capable hospital, the door-to-balloon time should be within 90 minutes. The treatment options and time recommended after first hospital arrival are the same. (Adapted from Armstrong PW, Collen D, Antman E: Fibrinolysis for acute myocardial infarction: The future is here and now. Circulation 2003;107:2533-7, with permission.)

ECG is not diagnostic, the patient remains symptomatic, and there is a high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous ST-segment monitoring should be performed. The choice of initial STEMI treatment should be made by the Emergency Medicine physician on duty in the ED based on a predetermined, institution-specific, written protocol. If the initial diagnosis and treatment plan are not clear, immediate cardiology consultation should be obtained.

Patient Evaluation

A targeted history should ascertain whether the patient has had prior stable or unstable angina, myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, or PCI. Evaluation of the patient's complaints should focus on chest discomfort, associated symptoms, gender- and age-related differences in presentation, hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding, and clinical cerebrovascular disease (amaurosis fugax, face/limb weakness or clumsiness, sensory loss, ataxia, or vertigo). A brief targeted physical examination should focus on potential complications of STEMI. A differential diagnosis should be reviewed to exclude other conditions that may mimic STEMI.

The 12-lead ECG in the ED is at the center of the therapeutic decision pathway. The risk of mortality increases with the number of ECG leads that show ST-segment elevation and with the sum of ST-segment deviation in 12 leads.[28] Important predictors of mortality include anterior location and left bundle branch block (LBBB). Patients with ≥0.1 mV ST-elevation in two contiguous leads are candidates for reperfusion therapy. Patients with inferior STEMI should have right-sided leads obtained to screen for ST-elevation suggestive of right ventricular (RV) infarction. Although patients without ST-elevation should not be treated with fibrinolytic therapy, its use is appropriate when there is marked ST-segment depression confined to leads V1 through V4 and accompanied by tall R waves in the right precordial leads and upright T waves indicative of a true posterior injury current.[29] Patients with new or presumed new LBBB and signs and symptoms of STEMI should also be considered for reperfusion therapy.

Laboratory examinations should include serial cardiac biomarkers (CK-MB, troponins) for cardiac damage, CBC, platelet count, INR, aPTT, electrolytes, magnesium, BUN, creatinine, glucose, and serum lipids. Therapeutic decisions should not be delayed until these results are returned. Cardiac biomarkers are useful for confirming the diagnosis of STEMI, assessing the success of fibrinolytic therapy, estimating infarct size, and providing prognostic information.

Several imaging tests can be used to evaluate patients with chest pain. A portable chest radiograph should be obtained, but should not delay initiation of reperfusion therapy. Transthoracic and/or transesophageal echocardiography is useful for evaluating ventricular function and diagnosing mechanical complications. A contrast chest CT may be required to exclude aortic dissection. CT angiography and magnetic resonance imaging are investigational techniques. Radionuclide imaging is not indicated in the acute setting.

Routine Measures

Oxygen

Supplemental oxygen should be administered by nasal prongs for at least 6 hours because of possible ventilation-perfusion mismatch or excessive lung water.[30] It should be discontinued after 6 hours if the arterial saturation is >90%. In patients with severe CHF, pulmonary edema, or mechanical complications, endotracheal intubation and mechanical ventilation may be required.

Nitroglycerin

Nitrates are indicated to relieve ischemic pain, control hypertension, and as a vasodilator in patients with LV failure or coronary spasm. Clinical trial results have suggested only a modest benefit from nitroglycerin therapy. A pooled analysis of more than 60,000 patients treated with nitrate-like preparations intravenously or orally in 22 trials revealed a mortality rate of 7.7% in the control group, that was reduced to 7.4% in the nitrate group. These data are consistent with a possible small treatment effect of nitrates on mortality rates (3 to 4 fewer deaths for every 1000 patients treated).[31]

Nitrates should be avoided in patients with initial systolic blood pressures <90 mm Hg, marked bradycardia or tachycardia, and in patients with known or suspected right ventricular infarction.[32] Phosphodiesterase inhibitors potentiate the hypotensive effects of nitrates by releasing nitric oxide.[33] Therefore, nitrates should not be administered to patients who have used a phosphodiesterase inhibitor for erectile dysfunction in the preceding 24 to 48 hours.

Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of 3 doses, after which an assessment should be made about the need for intravenous administration. A useful intravenous regimen employs an initial infusion rate of 5 to 10 mcg per minute with increases of 5 to 20 mcg per minute until symptoms are relieved or mean arterial blood pressure is reduced by 10% of its baseline level in normotensive patients and by up to 30% in hypertensive patients. In no case should the systolic pressure be brought below 90 mm Hg or drop 30 mm Hg below baseline. In view of their marginal treatment benefits, nitrates should not be used if hypotension limits the administration of β-blockers or ACE inhibitors, which have more powerful salutary effects.

Analgesia

The clinician should focus on two aspects of pain management (1) acute relief of the symptoms of ongoing myocardial ischemia and necrosis; and (2) the general relief of anxiety and apprehension that frequently exacerbate pain. Pain, which is commonly severe in the acute phase of STEMI, contributes to the hyperadrenergic state that has been implicated as having a role in plaque fissuring and thrombus propagation, and in reducing the threshold for ventricular fibrillation.

The tendency to underdose patients should be avoided. Control of cardiac pain is typically accomplished with a combination of nitrates, opiate analgesic agents, oxygen, and β-blockers. Morphine sulfate has remained the analgesic agent of choice for STEMI patients. The dose required varies in relation to age and body size as well as to blood pressure and heart rate. Morphine sulfate (2 to 4 mg intravenously with increments of 2 to 8 mg intravenously, repeated at 5 to 15 minute intervals) may be given to a total dose of 10 to 30 mg as necessary. Morphine administration is particularly helpful in acute pulmonary edema where it may promote peripheral arterial and venous dilatation. An important consideration when using intravenous nitrates is not to lower blood pressure to a level that would preclude adequate dosing of morphine.

Side effects of morphine administration, such as hypotension, can be minimized by keeping the patient supine and elevating the lower extremities if systolic pressure drops below 100 mm Hg. The concomitant use of atropine in 0.5 mg doses intravenously may be helpful in reducing the excessive vagomimetic effects of morphine if significant bradycardia or hypotension occurs. Although respiratory depression is relatively uncommon, the respiration rate should be monitored, particularly as cardiovascular status improves. The narcotic reversing agent naloxone, 0.4 to 2 mg intravenously every 3 minutes up to 10 mg, can reverse the effects of morphine should respiratory compromise occur. Nausea and vomiting as potential side effects of large doses of morphine may be treated with a phenothiazine.

Antiplatelet Agents

Aspirin

In the ISIS-2 trial,[34] aspirin reduced 35-day mortality by 23%. When aspirin was combined with streptokinase, the relative reduction in mortality was 42%. A meta-analysis demonstrated that aspirin reduced coronary reocclusion and recurrent ischemic events after fibrinolytic therapy with either streptokinase or alteplase.[35] The initial dose should be 162 to 325 mg, and it should be continued indefinitely at a daily dose of 75 to 162 mg. This dose has been found to be as effective as higher doses and with less toxicity.[36] Aspirin suppositories (300 mg) can be used safely for patients with severe nausea and vomiting or with severe upper gastrointestinal problems. In patients with true aspirin hypersensitivity (hives, nasal polyps, bronchospasm, or anaphylaxis), clopidogrel or ticlopidine may be substituted with at least equal effectiveness.[37] The use of ibuprofen or other NSAIDs may limit the cardioprotective effect of aspirin.

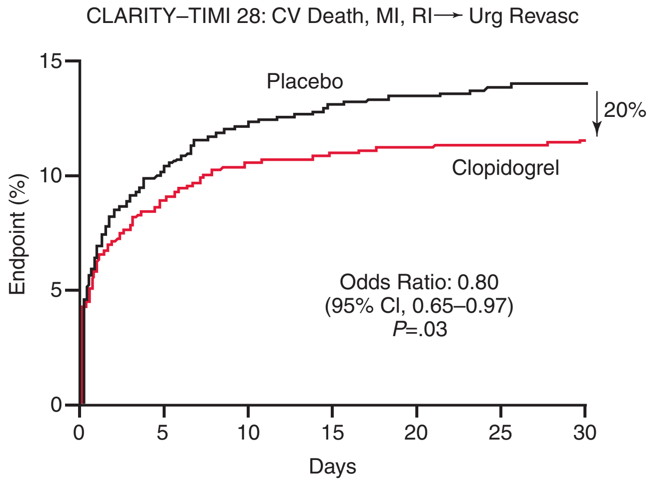


Figure 11–3 Cumulative incidence of the endpoint of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization. The odds ratio for this endpoint was significantly lower in the clopidogrel group than in the placebo group at 30 days (11.6% versus 14.1%; odds ratio, 0.80 [95% confidence interval, 0.65 to 0.97]; *P* = 0.03). (Adapted from Sabatine MS, Cannon CP, Gibson CM, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST segment elevation. N Engl J Med 2005;352:1179-89, with permission.)

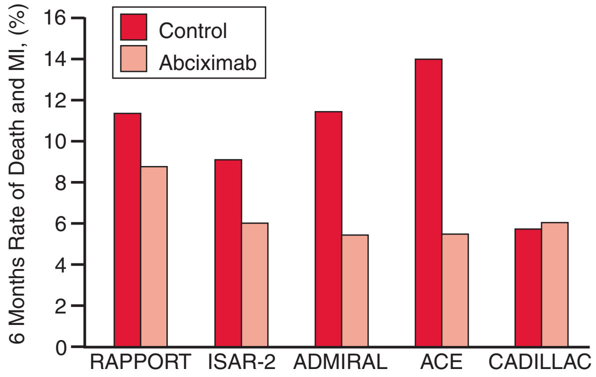


Figure 11–4 Rates of death and myocardial infarction (MI) at 6 months for five trials of primary percutaneous coronary intervention (PCI) with and without abciximab. (Adapted from Topol EJ, Neumann FJ, Montalescot G: A preferred reperfusion strategy for acute myocardial infarction. J Am Coll Cardiol 2003;42:1886-9, with permission.)

Clopidogrel

The COMMIT/CCS-2 trial[38] demonstrated a 13% reduction in death, MI, and stroke in medically managed patients treated within 12 hours of symptom onset with clopidogrel 75 mg daily. The CLARITY-TIMI 28 trial[39] demonstrated a 20% reduction in death, MI, and urgent revascularization in medically managed patients treated with a 300-mg loading dose of clopidogrel and a 75-mg daily maintenance dose as part of an early invasive strategy in patients <75 years old (Fig. 11–3). Neither trial showed an increase in major bleeding or intracranial hemorrhage. Therefore, patients should receive clopidogrel whether or not they are treated with PCI for at least 1 month (loading dose of 300 mg in patients <75 years of age who receive fibrinolysis and a loading dose of 75 mg in patients >75 years of age regardless of whether fibrinolysis is administered). It should be continued for at least 3 months after sirolimus drug-eluting stent implantation, 6 months after paclitaxel drug-eluting stent implantation, and up to 12 months in patients who are not at high risk for bleeding. For patients on clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days, and preferably for 7 days, unless the urgent need for revascularization outweighs the risk of excess bleeding.[40]

GP IIb/IIIa Inhibitors

Abciximab in combination with fibrinolytic therapy did not improve survival in two trials.[41,42] It did reduce reinfarction rates in patients <75 years old with anterior STEMI, but it increased ICH rates in older patients. Intravenous GP IIb/IIIa receptor inhibitors have also been studied as supportive antiplatelet therapy in patients who are undergoing PCI. Five randomized trials compared abciximab with placebo in patients who were undergoing primary PCI.[43-47] Treated patients had fewer adverse cardiac events (Fig. 11–4). The benefit appeared greater in patients treated before arrival at the cardiac catheterization laboratory because of higher initial patency rates.[45] Abciximab had greater benefit in patients receiving PTCA than stenting in the CADILLAC trial,[46] but decreased the risk of subacute stent thrombosis during follow-up. There are limited data on eptifibatide and tirofiban, but because of a similar mechanism of action, they may also be useful as antiplatelet therapy.

Antithrombin Agents

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are antithrombins, and they decrease the rates of infarct artery reocclusion, deep venous thrombosis, pulmonary embolism, LV mural thrombus formation, and cerebral embolization. Anticoagulation is recommended in patients not receiving reperfusion therapy because data from the prefibrinolytic era demonstrate benefit in the absence of other interventions.[48]

Because streptokinase produces a systemic coagulopathy, additional antithrombin therapy with UFH offers only the small advantage of five lives saved per 1000 patients treated at a cost of one to two hemorrhagic strokes and three to five systemic bleeds (Fig. 11–5).[48] Therapy is most useful in patients at high risk for systemic embolism including those patients with large or anterior MI, atrial fibrillation, previous embolism, or known LV thrombus. With fibrin-specific agents (alteplase, reteplase, tenecteplase), UFH should be given intravenously with an aPTT target of 1.5 to 2.0 times control (50 to 70 seconds). A 60 U/kg bolus followed by a maintenance infusion of 12 U/kg per hour (with a maximum of 4000 U bolus and 1000 U/hour initial infusion for patients weighing >70 kg) is recommended. A bolus dose of 70 to 100 U/kg with a target activated clotting time of 300 seconds is recommended for primary PCI. The bolus dose should be reduced to 50 to 70 U/kg to achieve an ACT of 200 seconds when GP IIb/IIIa agents are used or rescue PCI is being performed.

The CREATE trial demonstrated that reviparin was superior to placebo in reducing the composite endpoint of death, MI, or stroke.[48a] LMWH can be considered an acceptable alternative to UFH as ancillary therapy to fibrinolysis, provided

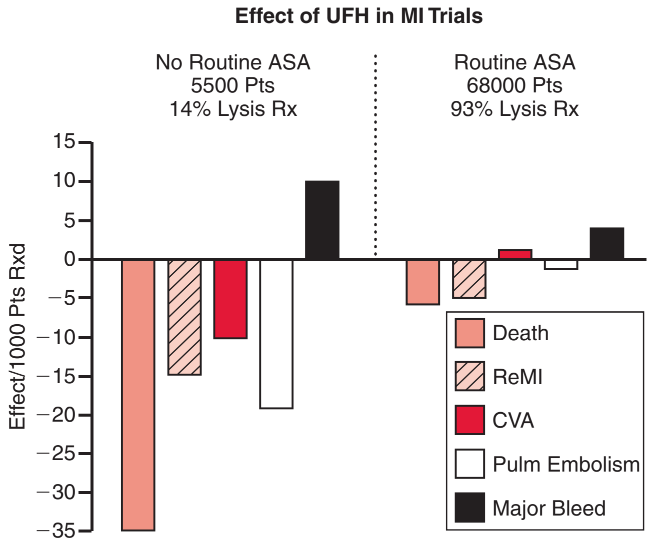


Figure 11–5 Effect of unfractionated heparin (UFH) in STEMI trials. The treatment effect of UFH/1000 patients is shown for trials without routine aspirin (ASA) *on the left* and with routine ASA *on the right.* Benefits of UFH are plotted *below the horizontal line* and harm is plotted *above the line.* CVA, cerebrovascular accident; Pulm Embolism, pulmonary embolism; ReMI, recurrent myocardial infarction; STEMI, ST-elevation myocardial infarction. (Adapted from data in Collins R, Peto R, Baigent C, Sleight P: Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. N Engl J Med 1997;336:847-60, with permission.)

significant renal dysfunction (serum creatinine >2.5 mg/dL in men or 2.0 mg/dL in women) is not present. Enoxaparin (30 mg intravenous bolus followed by 1.0 mg/kg subcutaneously every 12 hours until hospital discharge) used in combination with full-dose tenecteplase until recently was the most comprehensively studied regimen in patients <75 years of age.[42] However, older patients have an unacceptable excess rate of ICH with this dose.[49] The ExTRACT-TIMI 25 trial tested a reduced dose of enoxaparin (no intravenous bolus; maintenance dose of 0.75 mg/kg every 12 hours) in elderly patients.[49a] When combined with clopidogrel, LMWH is associated with significantly improved rates of angiographic patency and lower rates of death/MI compared with UFH.[50] In ExTRACT-TIMI 25, there was a 17% relative risk reduction in the composite endpoint of death or nonfatal reinfarction and a 19% relative risk reduction in the composite endpoint of death or nonfatal reinfarction or urgent revascularization with enoxaparin compared with unfractionated heparin ($P < 0.001$) (Fig. 11–6).[49b] Major bleeding occurred in 2.1% and 1.4% of the enoxaparin and unfractionated heparin groups, respectively ($P < 0.001$). The direct thrombin inhibitor bivalirudin was not superior to UFH in patients receiving streptokinase,[51] but may be an option in patients with known heparin-induced thrombocytopenia who need anticoagulation.

The OASIS-6 trial evaluated the specific factor Xa antagonist fondaparinux (2.5 mg subcutaneously daily) in 12,092 patients with STEMI.[51a] The trial design compared fondaparinux given for up to 8 days versus placebo in patients when the treating physician felt UFH was not indicated (stratum I) and versus unfractionated heparin for 48 hours when the treating physician felt UFH was indicated (stratum II). The primary endpoint, death, or reinfarction, occurred in 14% of placebo patients and 11.2% of fondaparinux patients in stratum I (HR 0.79; 0.68-0.92), and in 8.7% of UFH patients and 8.3% of fondaparinux patients (HR 0.96; 0.81-1.13) in stratum II. Thus, fondaparinux was superior to placebo (stratum I) but yielded similar results to those achieved with UFH (stratum II). The outcome of patients in stratum II who underwent PCI tended to be worse when fondaparinux was used. Severe hemorrhage occurred in 1.3% of control patients and 1.0% of fondaparinux patients through nine days (p = 0.13). While the convenience of once-daily subcutaneous injections of fondaparinux may be attractive compared with UFH, the need for co-administration of an additional antithrombin with antiIIa activity if a PCI is performed in a patient treated with fondaparinux complicates its use.[51b] Further information regarding the appropriate dosing of additional antithrombins along with fondaparinux in the catheterization laboratory, as well as additional information regarding the benefits and risks of fondaparinux across a broad range of fibrinolytics, is needed before its role in the management of STEMI can be properly established.

β-Blockers

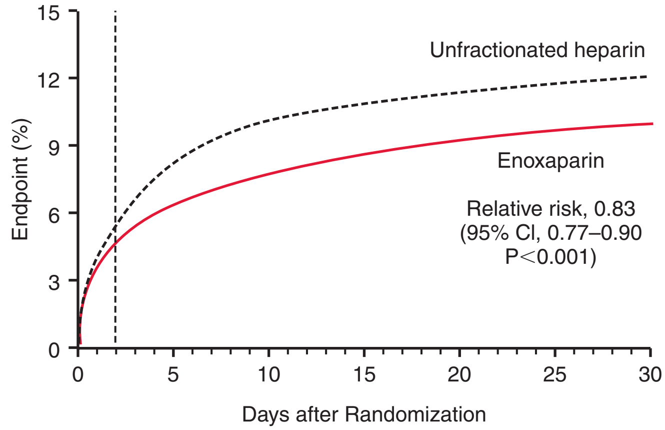
β-Blockers diminish myocardial oxygen demand by reducing heart rate, systemic arterial pressure, and myocardial contractility. Reduction in the heart rate prolongs the diastolic period and may augment perfusion to the subendocardium. In patients not receiving fibrinolytic therapy, early trials suggested reduction in infarct size[52] and mortality.[53,54] In patients receiving fibrinolytic therapy, trials have not found a mortality reduction,[55,56] although recurrent ischemia and reinfarction rates were reduced. It has also been suggested that β-blockers decrease ventricular arrhythmias and decrease the risk of intracerebral hemorrhage with lytic therapy. Therefore, it is reasonable to give early intravenous β-blockade to STEMI patients without contraindications, followed by oral therapy.

Intravenous metoprolol is given in three 5 mg doses over 15 minutes, followed by a 25 to 50 mg oral dose 15 minutes later and every 6 hours for 48 hours, before twice daily administration of 50 to 100 mg. Intravenous atenolol is given as two 5 mg doses 15 minutes apart. Then, 50 mg is given orally 15 minutes later, followed by another 50 mg in 12 hours and then 50 to 100 mg daily. Contraindications to the use of early intravenous and oral β-blockade include heart rate <60 beats per minute, systolic arterial pressure <100 mm Hg, uncompensated CHF or cardiogenic shock, PR interval >24 seconds, second or third degree AV block, active asthma or reactive airways disease, and cocaine use. If bradycardia or hypotension occurs with therapy, isoproterenol 1 to 5 mcg/min can be administered. Administration of early β-blocker therapy to patients with pump failure increases mortality rates.[38a]

Reperfusion Therapy

General Concepts

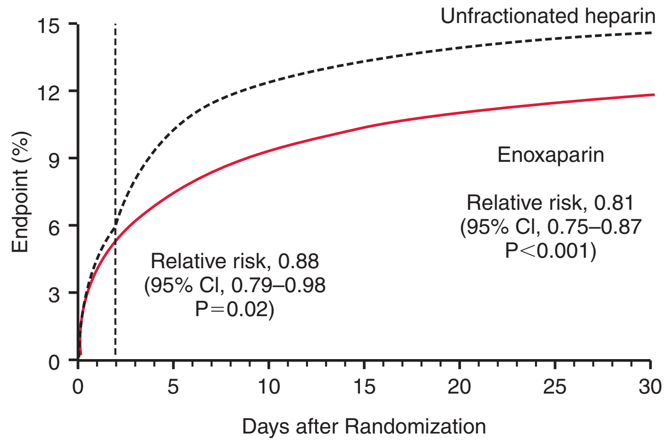
All STEMI patients should undergo rapid evaluation for reperfusion therapy and have a reperfusion strategy implemented promptly after contact with the medical system. Although rapid spontaneous reperfusion of the occluded infarct artery may occur, restoration of flow usually requires either fibrinolytic therapy or PCI. Many comparisons of these two reperfusion strategies have treated them as competing



A

No. at Risk

Unfractionated heparin	10,223	9,385	9,188	9,109	9,064	9,027	8,994
Enoxaparin	10,256	9,595	9,460	9,362	9,301	9,263	9,234



B

No. at Risk

Unfractionated heparin	10,223	9,174	8,955	8,868	8,818	8,775	8,738
Enoxaparin	10,256	9,479	9,312	9,200	9,130	9,084	9,052

Figure 11–6 Cumulative incidence of the primary endpoint (**A**) and the secondary endpoint (**B**). In **A,** the rate of the primary endpoint (death or nonfatal myocardial infarction) at 30 days was significantly lower in the enoxaparin group than in the unfractionated heparin group (9.9% versus 12.0%, $P < 0.001$ by the log-rank test). The *dashed vertical line* indicates the comparison at day 2 (direct pharmacologic comparison), at which time a trend in favor of enoxaparin was seen. In **B,** the rate of the main secondary endpoint (death, nonfatal myocardial infarction, or urgent revascularization) at 30 days was significantly lower in the enoxaparin group than in the unfractionated heparin group (11.7% versus 14.5%, $P < 0.001$ by the log-rank test). The difference was already significant at 48 hours (6.1% in the unfractionated heparin group versus 5.3% in the enoxaparin group, $P = 0.02$ by the log-rank test). The interval shown is the time (in 24-hour intervals) from randomization to an event or the last follow-up visit. CI, confidence interval. (Adapted from Antman EM, Morrow DA, McCabe CH, et al., for the ExTRACT-TIMI 25 Investigators: Enoxaparin versus unfractionated heparin with fibrinolysis for ST-Elevated Myocardial Infarction. N Engl J Med 2006;354:1477-88, with permission.)

options with little consideration of an interface between them (Fig. 11–7). Early, complete, and sustained infarct artery patency is a key determinant of both short- and long-term prognosis regardless of whether reperfusion is accomplished by fibrinolysis[23] or by PCI.[57] Therefore, every effort should be made to shorten the time from symptom onset to contact with the medical system and to implement a reperfusion strategy using the concept of medical system goals. These include a door-to-needle (or EMS-to-needle) time for fibrinolytic therapy within 30 minutes or a door-to-balloon (or EMS-to-balloon) time for PCI within 90 minutes. These goals should not be understood as *ideal* times, but rather the longest times that should be considered acceptable in every appropriate patient unless there is a good reason for delay, such as uncertainty about the diagnosis, need for the evaluation and treatment of other life-threatening conditions (e.g., respiratory failure), or delays associated with the patient's informed choice to consider therapy.

Even when fibrinolysis or PCI is successful in restoring infarct artery flow, perfusion of the infarct zone may still be compromised by a combination of microvascular damage and reperfusion injury.[58] Microvascular damage results from downstream thrombus embolization followed by the release of substances from activated platelets that promote microvascular spasm. Reperfusion injury results in cellular edema, free radical formation, calcium overload, and acceleration of apoptosis. Additionally, cytokine activation in the infarct zone leads to neutrophil accumulation and inflammatory mediators that contribute to tissue injury. Thus, adjunctive and ancillary treatments that minimize the amount of microvascular damage and also protect the jeopardized myocardial infarct zone are needed for more successful tissue-level reperfusion.

Four variables should be considered in selecting the type of reperfusion therapy (1) time from symptom onset; (2) risk of STEMI; (3) risk of fibrinolysis; and (4) predicted door-to-balloon time.

Time from Symptom Onset

Fibrinolytic therapy administered within the first two (especially the first) hours can occasionally abort MI and dra-

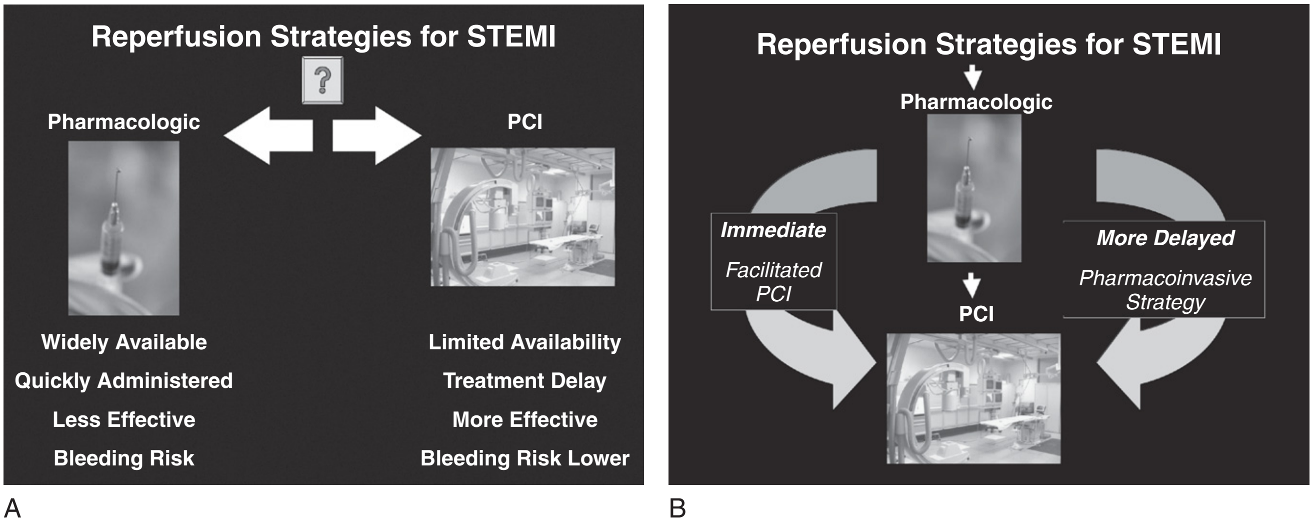


Figure 11–7 Reperfusion strategies for ST-elevation myocardial infarction (STEMI). **A,** Strategies where fibrinolytic therapy is selected versus percutaneous coronary intervention (PCI). **B,** Strategies where a pharmacologic regimen is given before PCI.

matically reduces mortality rates.[22,23] Prehospital fibrinolysis reduces treatment delays by up to 1 hour, allowing the majority of patients to be treated within 2 hours of symptom onset, and reduces mortality rates by 17% compared with therapy initiated in the hospital.[59] However, the efficacy of fibrinolytic agents in lysing thrombus diminishes with increasing treatment delays.[60] In contrast, PCI can seldom be performed within 2 hours of symptom onset, but reperfusion rates are superior to fibrinolytic therapy and independent of time. Although the CAPTIM[61] and PRAGUE-2[62] studies reached different conclusions about the overall superiority of PCI over fibrinolysis, similar results were seen in time-to-treatment subset analyses. Patients treated within 2 hours of symptom onset in CAPTIM had improved outcomes with prehospital tPA versus transfer for PCI.[63] Patients treated within 3 hours of symptom onset in PRAGUE-2 had equivalent mortality rates whether treated with streptokinase or transferred for PCI.[62] Conversely, both studies showed superior outcomes with PCI in patients with symptom duration >3 hours.

Risk of STEMI

Different risk stratification tools are available to quantify risk.[64,65] Patients with low mortality risk have similar outcomes with fibrinolysis or PCI.[66,67] Patients with anterior STEMI,[66,67] older age, congestive heart failure,[68] or cardiogenic shock[69] have better outcomes with PCI. The point of equipoise between strategies is an estimated 30-day mortality risk of 3%.[70]

Risk of Bleeding

The higher the risk of bleeding with fibrinolytic therapy, the more PCI would be favored as the reperfusion strategy. The increased risk for ICH in the elderly is a strong factor that favors PCI in this subgroup.

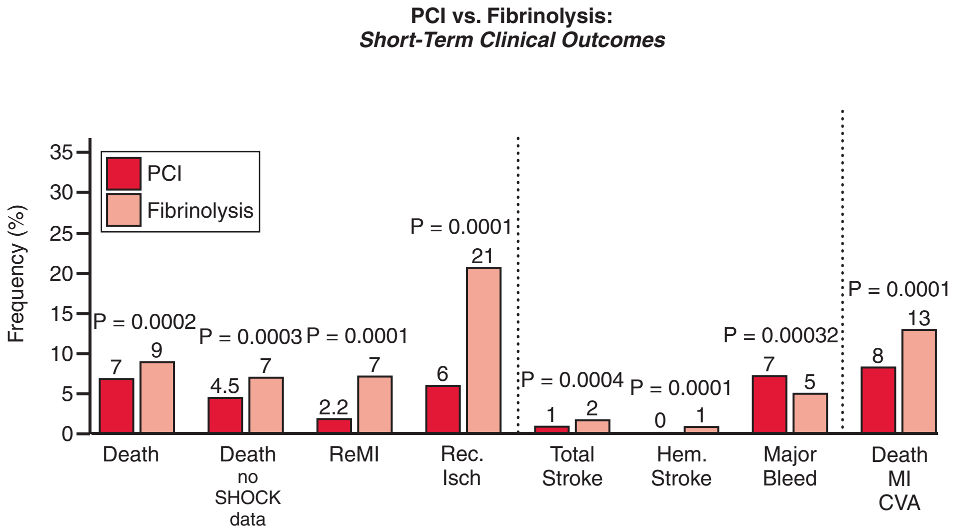
Predicted Door-to-Balloon Time

PCI is superior to fibrinolytic therapy when it can be performed expeditiously by experienced teams in high-volume hospitals.[71] The benefit noted in the randomized clinical trials[72] (Fig. 11–8) was strongly influenced by a reduction of nonfatal recurrent MI. This benefit was likely exaggerated by protocols that strongly discouraged rescue PCI when fibrinolysis failed or cardiac catheterization for recurrent ischemia after initially successful fibrinolysis. Nevertheless, stroke and mortality rates were lower with PCI, and clinical experience supports less complicated hospitalizations and fewer hospital days for these patients. However, complication rates are higher for patients who present after routine working hours,[73] and lower mortality rates with PCI have not been demonstrated in low-volume hospitals.[71,74] In hospitals without PCI capability, the reperfusion therapy choice is fibrinolytic therapy or transfer to a PCI center. Because the mortality benefit associated with PCI over fibrinolysis decreases as time-to-treatment differences increase,[75] the PCI strategy may not reduce mortality when a treatment delay >60 minutes is anticipated (Fig. 11–9). In the United States, only 4% of transfer patients are treated with PCI within 90 minutes and the average time to treatment is 3 hours.[76] Therefore, STEMI patients who present to a facility that does not have the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact should undergo fibrinolysis unless contraindicated.[2] Clinical circumstances in which fibrinolytic therapy or PCI are generally preferred are shown in Table 11–1.

Fibrinolytic Therapy

Indications and Contraindications

In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation >0.1 mV in at least two contiguous leads or new, or presumably new, LBBB. Patients with true posterior MI and patients with symptom duration for 12 to 24 hours and ST elevation are also reasonable candidates. Contraindications and cautions for using fibrinolytic therapy are shown in Table 11–2. Hemorrhage is the most critical risk, especially intracranial hemorrhage which is fatal in more than one half of patients. Several models for estimating the risk of ICH after fibrinolysis have been developed.[77-79] Patients with >4% risk of ICH should be treated with PCI rather than fibrinolytic therapy. Streptokinase without heparin has the lowest ICH rate.



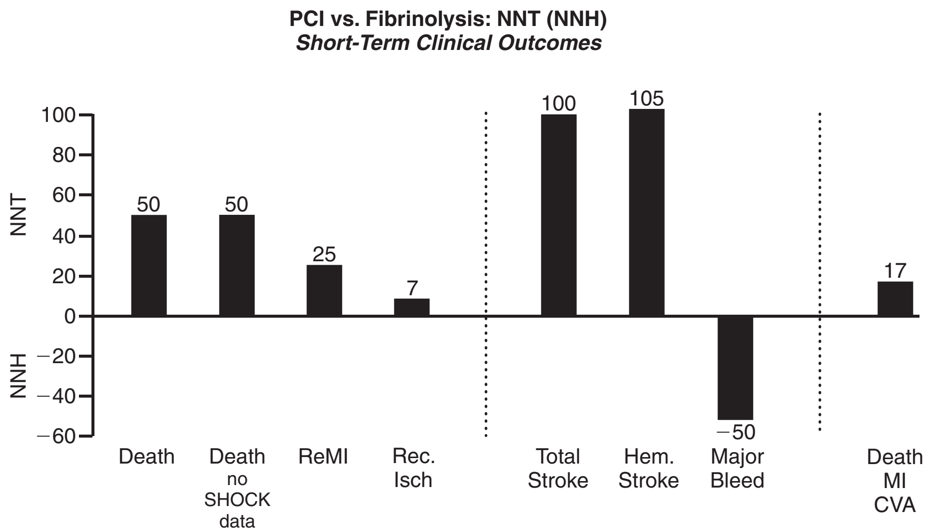


Figure 11–8 Percutaneous coronary intervention (PCI) versus fibrinolysis for ST-elevation myocardial infarction (STEMI). The short-term (4 to 6 weeks) (*top left*) and long-term (*top right*) outcomes for the various endpoints shown are plotted for patients with STEMI randomized to PCI or fibrinolysis for reperfusion in 23 trials ($N = 7739$). Based on the frequency of events for each endpoint in the two treatment groups, the number needed to treat (NNT) or number needed to harm (NNH) is shown for the short-term (*bottom left*) and long-term (*bottom right*) outcomes. The magnitude of the treatment differences for death, nonfatal reinfarction, and stroke vary depending on whether PCI is compared with streptokinase or a fibrin-specific lytic. For example, when primary PCI is compared with alteplase (tPA) and the SHOCK trial is excluded, the mortality rate is 5.5% versus 6.7% (OR 0.81, 95% CI 0.64 to 1.03, $P = 0.081$). CVA, cerebrovascular accident; Hem. Stroke, hemorrhagic stroke; MI, myocardial infarction; Rec. Isch, recurrent ischemia; ReMI, recurrent MI. (Adapted from Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet 2003;361:13-20, with permission.)

Mortality Benefit

Placebo controlled trials have demonstrated the survival benefit associated with fibrinolytic therapy.[34,80-82] Mortality reduction is greatest within the first few hours of symptoms, especially the first hour, due to salvage of ischemic myocardium with reduced infarct size. The mortality benefit that is seen with later treatment is more dependent on improved infarct healing and myocardial remodeling, on reduced electrical heterogeneity, and on the reduced potential for life-threatening ventricular arrhythmia. Patients with LBBB, anterior MI, hypotension, and tachycardia have higher risk from STEMI and achieve greater therapeutic benefit.[22] The patient risk and potential therapeutic benefit in inferior MI are increased with right ventricular involvement, precordial ST depression, or complete heart block.[83] The number of ECG leads involved and the extent of ST deviation is an excellent predictor of potential STEMI risk.[28] Although patients more than 75 years of age might better be treated with PCI, the absolute number of lives saved per 1000 patients treated with fibrinolytic therapy compared with placebo is actually greater than in younger patients (34 versus 28).[84]

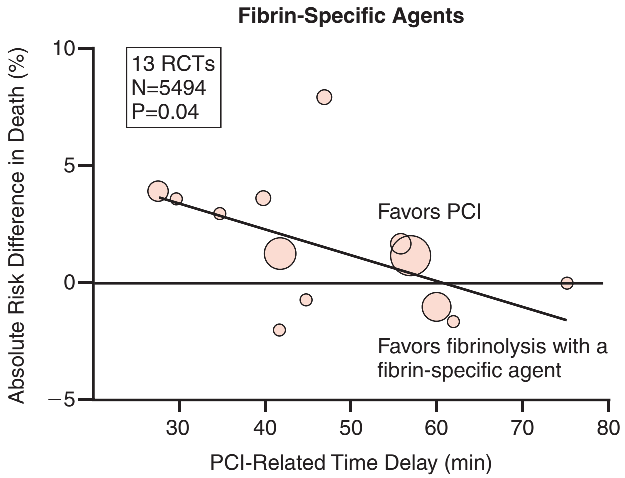


Figure 11–9 PCI versus lysis with fibrin-specific agents: Is timing (almost) everything? RCT, randomized controlled trial; N, number of patients; PCI, percutaneous coronary intervention. (Adapted from Nallamothu BK, Bates ER: Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: Is timing (almost) everything? Am J Cardiol 2004;94:772-4, with permission.)

Effect on LV Function

Successful early reperfusion reduces infarct size, preserves regional wall motion, decreases ventricular dilation, and maintains global left ventricular function—an important predictor of survival. Restoration of normal infarct artery flow does not reflect microvascular reperfusion, which is better evaluated by myocardial blush on angiography, contrast perfusion on echocardiography, or prompt resolution of ST elevation on electrocardiography. Poor microvascular reperfusion is associated with increased infarct size, morbidity, and mortality.

Complications

The major complication of fibrinolytic therapy is hemorrhage which may or may not require transfusion. Risk factors include older age, female gender, lower body weight, and hypertension. Intracerebral hemorrhage encompasses parenchymal hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, subdural hematoma, and epidural hematoma. Typical presenting features include an acute change in level of consciousness, unifocal or multifocal neurologic signs, coma, headache, nausea, vomiting, and seizures. The occurrence of a change in neurologic status during or after reperfusion therapy, particularly within the first 24 hours after initiation of treatment, is considered to be due to ICH until proved otherwise (Fig. 11–10). Fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until a brain imaging scan shows no evidence of ICH. Neurology and/or neurosurgery consults should be obtained as dictated by clinical circumstances. Immediate measures to reduce intracranial pressure include mannitol infusion, elevation of the head of the bed to 30 degrees, endotracheal intubation, and hyperventilation to achieve a P_{CO_2} of 25 to 30 mm Hg. Cryoprecipitate (10 U) will increase the fibrinogen level by approximately 0.70 g/liter and the factor VIII level by approximately 30% in a 70-kg adult. Fresh frozen plasma restores factors V and VIII levels. Protamine (1 mg/100 U of UFH given in the preceding 4 hours) reverses heparin anticoagulation. Platelet transfusions (6 to 8 units) can be given if the bleeding time is abnormal. Blood pressure and blood glucose levels should be optimized. Neurosurgical evacuation of ICH may be required in select patients.[85]

Table 11–1 Assessment of Reperfusion Options for Patients with STEMI

Step 1: Assess Time and Risk

- Time since onset of symptoms
- Risk of STEMI
- Risk of fibrinolysis
- Time required for transport to a skilled PCI lab

Step 2: Determine if Fibrinolysis or an Invasive Strategy is Preferred

If presentation is <3 hours and there is no delay to an invasive strategy, there is no preference for either strategy.

Fibrinolysis is generally preferred if

- Early presentation (≤3 hours from symptom onset) and delay to invasive strategy (see below)
- Invasive Strategy is not an option
  - Catheterization lab occupied/not available
  - Vascular access difficulties
  - Lack of access to a skilled PCI lab†‡
- Delay to Invasive Strategy
  - Prolonged transport
  - Door-to-Balloon–Door-to-Needle time is >1 hour*§
  - Medical Contact-to-Balloon or Door-to-Balloon time is >90 minutes

An invasive strategy is preferred if

- Skilled PCI lab available with surgical back-up†‡
  - Medical Contact-to-Balloon or Door-to-Balloon time is <90 minutes
  - Door-to-Balloon—Door-to-Needle time is <1 hour*
- High Risk from STEMI
  - Cardiogenic shock
  - Killip class is ≥3
- Contraindications to fibrinolysis including increased risk of bleeding and ICH
- Late presentation
  - The symptom onset was > 3 hours ago
- Diagnosis of STEMI is in doubt

*Applies to fibrin-specific agents.
†Operator experience > a total of 75 primary PCI cases/year.
‡Team experience > a total of 36 primary PCI cases/year.
§This calculation implies that the estimated delay to the implementation of the invasive strategy is >1 hour versus initiation of fibrinolytic therapy immediately with a fibrin-specific agent.
ICH, intracranial hemorrhage; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.
Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

Comparison of Fibrinolytic Agents

Fibrinolytic agents are plasminogen activators. Plasmin dissolves the fibrin mesh that holds red blood cells and platelets together as a thrombus. The four approved intravenous agents are compared in Table 11–3. Alteplase is superior

Table 11–2 Contraindications and Cautions for Fibrinolysis in STEMI*

Absolute Contraindications

- Any prior ICH
- Known structural cerebral vascular lesion (e.g., atrioventricular malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3 months

Relative Contraindications

- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP > 180 or DBP > 110 mm Hg)†
- History of prior ischemic stroke >3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)
- Recent (within 2-4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase/anistreplase: prior exposure or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

*Viewed as advisory for clinical decision-making and may not be all-inclusive or definitive.
†Could be an absolute contraindication in low-risk patients with myocardial infarction.
CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; ICH, intracranial hemorrhage; INR, international normalized ratio; SBP, systolic blood pressure.
Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;588-636.

to streptokinase in reducing morbidity and mortality, but is more expensive and confers a slightly higher risk of ICH.[86] Bolus dosing with reteplase[87] or tenecteplase[88] produces equivalent results compared with alteplase. The cost-benefit ratio is more favorable for the expensive agents in patients with a large myocardial area of risk and a low risk of ICH. Streptokinase is used by some clinicians when predicted infarct size is small or ICH risk is higher, but should not be reused because of the high prevalence of neutralizing antibody titers.

Percutaneous Coronary Intervention

Primary PCI

More than 90% of STEMI patients are candidates for primary PCI. Patency rates >90% and TIMI-3 flow rates of 70% to 90% have been reported. If immediately available, primary PCI should be performed in patients with STEMI (including true posterior MI) or MI with new or presumably new LBBB, who can undergo PCI of the infarct artery within 12 hours of symptom onset (or more than 12 hours if ischemic symptoms persist)—if performed in a timely fashion (balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (i.e., clinicians who perform more than 75 PCI procedures per year). The procedure should be supported by experienced personnel in an appropriate laboratory environment (that performs more than 200 PCI procedures per year, of which at least 36 are primary PCI for STEMI, and has cardiac surgery capability).[2]

Randomized clinical trials performed in selected patients by experienced providers demonstrated that PCI-treated patients experience lower short-term mortality rates (5.0% versus 7.0%, RR 0.70, 95% CI 0.58 to 0.85, $P = 0.0002$), less non-fatal reinfarction (3.0% versus 7.0%, RR 0.35, 95% CI 0.27 to 0.45, $P = 0.0003$), and less hemorrhagic stroke (0.05% versus 1.0%, RR 0.05, 95% CI 0.006 to 0.35, $P = 0.0001$) than those treated by fibrinolysis, but with an increased risk for major bleeding (7.0% versus 5.0%, RR 1.3, CI 1.02 to 1.65, $P = 0.032$) (see Fig. 11–8).[72] The efficacy differences are smaller when PCI is compared with alteplase, the invasive strategy is allowed after fibrinolytic therapy, patients are treated by less-experienced operators or in low-volume laboratories, or door-to-balloon times are excessively prolonged.

The survival benefit with PCI is time dependent (Fig. 11–11). To reproduce the outcomes in the randomized trials where PCI was performed by experienced operators with an additional mean treatment delay of 40 minutes for PCI instead of fibrinolytic therapy, strict performance criteria must be followed. These include door-to-balloon times <90 minutes, TIMI 2/3 flow rates in more than 90% of patients, emergency bypass surgery rates <2%, and performance of PCI in more than 85% of patients brought to the laboratory. Risk-adjusted hospital mortality rates should be <7% in patients without cardiogenic shock, which would be comparable with those reported for fibrinolytic therapy[72] and consistent with previously reported registry results where mortality rates were not different between treatment strategies.[25,89-91] If the performance criteria stated above cannot be met, fibrinolytic therapy should be considered unless it is contraindicated.

PCI has its greatest mortality benefit in high-risk patients. PCI has been associated with an absolute 9% reduction in 30-day mortality in cardiogenic shock[69] and a 33% relative risk reduction (versus 9% with fibrinolytic therapy) in congestive heart failure.[68] Compared with fibrinolytic therapy, PCI reduces mortality in patients with anterior MI, but there is no difference in patients with nonanterior MI.[66,67] Reocclusion rates are 15% after PTCA and 5% after stenting, compared with 30% after fibrinolytic therapy.[92] Potential complications include problems with the arterial access site; adverse reactions to volume loading, contrast medium, and antithrombotic medications; technical complications; and reperfusion events.

Compared with PTCA, intracoronary stents achieve a better immediate angiographic result with a larger arterial lumen, less reocclusion and restenosis of the infarct artery, and fewer subsequent ischemic events, but there are no differences in mortality rates or reinfarction rates.[93]

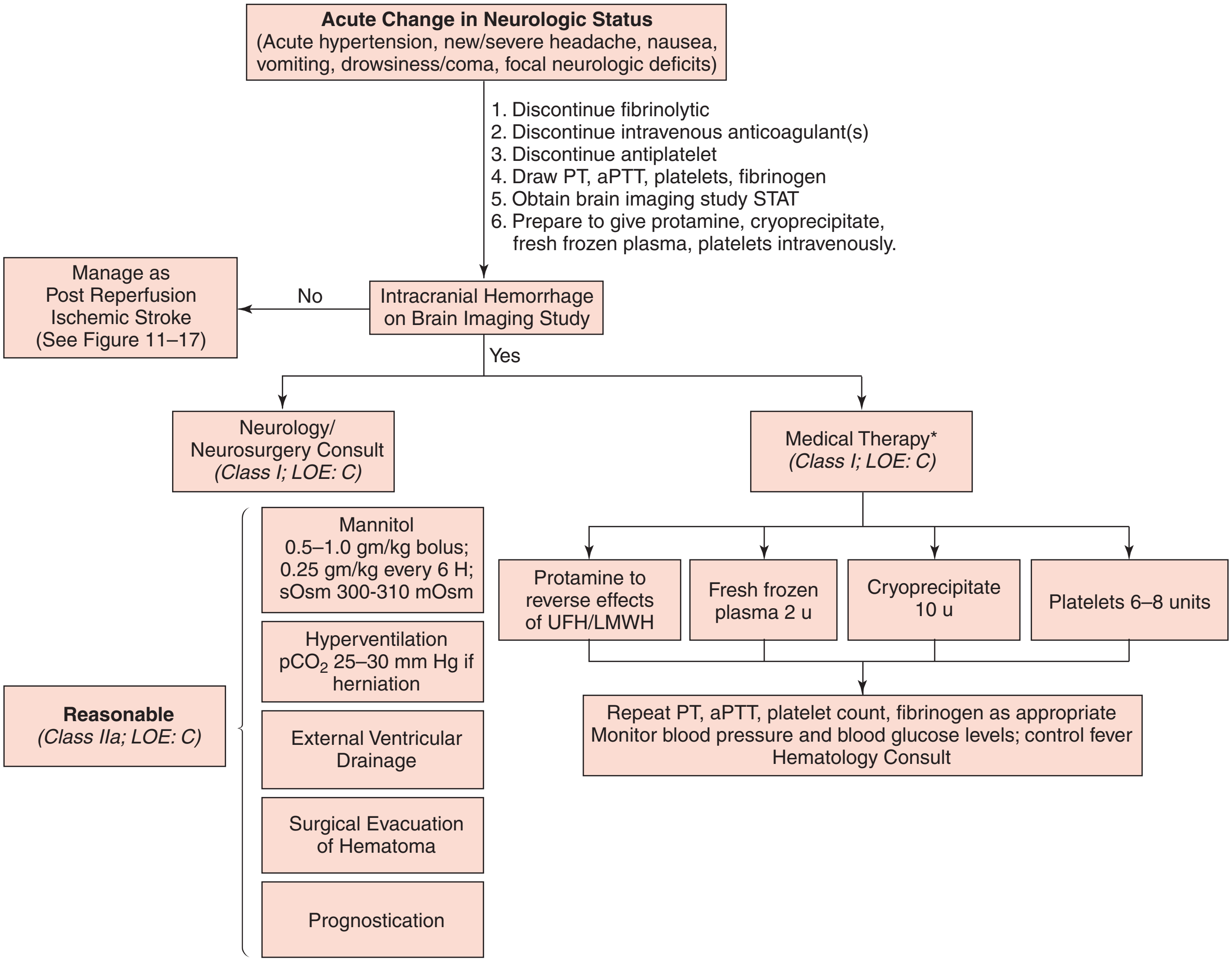


Figure 11–10 Algorithm for evaluation of intracranial hemorrhage complicating fibrinolytic therapy for ST-elevation myocardial infarction. *As dictated by clinical circumstances. aPTT, activated partial thromboplastin time; H, hours; LMWH, low-molecular-weight heparin; LOE, level of evidence; mOsm, milliosmoles; PT, prothrombin time; sOsm, serum osmolality; UFH, unfractionated heparin. (Adapted from The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group: A systems approach to immediate evaluation and management of hyperacute stroke: Experience at eight centers and implications for community practice and patient care. Stroke 1997;28:1530-40, with permission.)

Rescue PCI

Intravenous fibrinolytic therapy fails to restore infarct artery patency in 25% to 50% of patients. Rescue PCI can restore patency in most of these patients. A major challenge, however, is identifying patients with unsuccessful fibrinolysis and treating them within a time frame where myocardial salvage is possible. Clinical markers of reperfusion, such as relief of ischemic-type chest discomfort, partial resolution of ST-segment elevation, and reperfusion arrhythmias, have limited predictive value in identifying failure of fibrinolysis.[94] Other limitations of rescue PCI include higher rates of procedural failure, microvasular no-reflow, hemorrhage, and reocclusion than with primary PCI.

Rescue PCI in patients with anterior STEMI was previously shown to reduce congestive heart failure and death rates when performed within 8 hours of symptom onset.[95] Subsequently, rescue PCI was shown to reduce the combined 6-month endpoint of death, reinfarction, stroke, or severe heart failure by 50% compared with repeat fibrinolytic therapy or medical management in a general population.[96] Rescue PCI should be performed in patients with cardiogenic shock or congestive heart failure and is reasonable in patients with large infarction and persistent ischemic symptoms. The benefit in low-risk patients may not exceed the increased risk of bleeding.

Facilitated PCI

Facilitated PCI refers to a strategy of planned immediate PCI after an initial pharmacologic regimen such as full-dose fibrinolytic therapy, half-dose fibrinolytic therapy, a GP IIb/IIIa inhibitor, or a combination of reduced-dose fibrinolytic therapy and platelet GP IIb/IIIa inhibitor (see Fig. 11–7B). This represents a linear approach to reperfusion strategies rather than an either/or approach. It should be differentiated from drug administration during primary PCI and from rescue PCI after unsuccessful fibrinolysis. The theory is that earlier reperfusion will decrease infarct size before PCI stabilizes the index lesion. However, preliminary studies[97,98] have not demonstrated reduced infarct size or improved outcomes, and increased bleeding is a possibility. The ASSENT-4 PCI trial[99] demonstrated lower mortality (3.6% versus 6.0%)

Table 11–3 Comparison of Approved Fibrinolytic Agents

	Streptokinase	Alteplase	Reteplase	Tenecteplase-tPA
Dose	1.5 MU over 30-60 min	Up to 100 mg in 90 min (based on weight)*	10 U × 2 each over 2 min	30-50 mg (based on weight)†
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
90-min patency rates (approximate %)	50	75	75	75
TIMI grade 3 flow (%)	32	54	60	63
Cost (in dollars) per dose	$613	$2,974	$2,750	$2,833 for 50 mg

*Bolus 15 mg, infusion 0.75 mg/kg × 30 minutes (maximum 50 mg), then 0.5 mg/kg not to exceed 35 mg over the next 60 minutes to an overall maximum of 100 mg.
†30 mg for weight <60 kg; 35 mg for 60-69 kg; 40 mg for 70-79 kg; 45 mg for 80-89 kg; 50 mg for 90 kg or more.
MU, mega units; TIMI, Thrombolysis In Myocardial Infarction.
Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

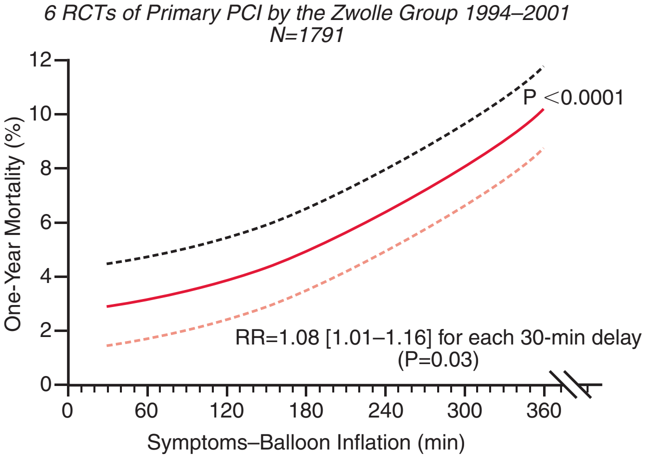


Figure 11–11 Symptom onset—balloon time and mortality in primary PCI for ST-elevation myocardial infarction. The relationship between time-to-treatment and 1-year mortality, as continuous functions, was assessed using a quadratic regression model. The *dotted lines* represent 95% confidence intervals of the predicted mortality. PCI, percutaneous coronary intervention; RCT, randomized controlled trial. (Adapted from De Luca G, Suryapranata H, Ottervanger JP, Antman EM: Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: Every minute of delay counts. Circulation 2004;109:1223-25, with permission.)

for primary PCI as compared with full-dose tenecteplase plus immediate catheterization owing to fewer ischemic complications, rather than fewer bleeding complications. However, in hospitals without PCI capability, the strategy still holds promise for high-risk patients who have low bleeding risk and short symptom duration. It is unlikely to be of benefit to low-risk patients, patients with immediate access to a catheterization laboratory, or those with longer symptom duration.

Hospitals Without On-Site Cardiac Surgery

Whereas hospitals with onsite cardiac surgery can offer immediate access to a PCI laboratory, hospitals without this resource have to establish more complicated treatment protocols that include interhospital transfer agreements. Fibrinolytic therapy will usually be the primary reperfusion strategy. However, many patients are ineligible for fibrinolytic therapy because of bleeding risk and should be considered for transfer for primary PCI.[100] Patients who fail fibrinolysis and are candidates for rescue PCI should also be transferred, as should patients with congestive heart failure or cardiogenic shock.

Some hospitals with cardiac catheterization laboratories are able to offer PCI without on-site cardiac surgery. Several performance criteria must be met for this strategy to reproduce the favorable results in published reports[101,102] (Table 11–4). The operators must be experienced interventionalists performing at least 75 interventions per year, the laboratory must perform at least 36 procedures per year, and the nursing and technical staff must be fully trained. The full range of PCI equipment must be available, and intra-aortic balloon counterpulsation expertise is required. Appropriate case selection and continuous quality improvement are important components (Table 11–5). High-risk patients should be transferred to a hospital with on-site surgery for primary PCI.

The concept of interhospital transfer for primary PCI versus on-site fibrinolytic therapy has been tested in five reports (Fig. 11–12).[62,103-106] The favorable results[107] were similar to those reported for primary PCI without interhospital transfer.[72] However, transfer times were short because of patient selection and a centrally organized emergency transportation system. To reproduce these results, the time from arrival at the first hospital door-to-balloon inflation in the

Table 11–4 Criteria for the Performance of Primary PCI at Hospitals Without On-Site Cardiac Surgery

- The operators must be experienced interventionalists who regularly perform elective PCI at a surgical center (at least 75 cases/year). The catheterization laboratory must perform a minimum of 36 primary PCI procedures per year.
- The nursing and technical catheterization laboratory staff must be experienced in handling acutely ill patients and comfortable with interventional equipment. They must have acquired experience in dedicated interventional laboratories at a surgical center. They participate in a 24-hour, 365-day call schedule.
- The catheterization laboratory itself must be well equipped, with optimal imaging systems, resuscitative equipment, IABP support, and must be well-stocked with a broad array of interventional equipment.
- The cardiac care unit nurses must be adept in hemodynamic monitoring and IABP management.
- The hospital administration must fully support the program and enable the fulfillment of the above institutional requirements.
- There must be formalized written protocols in place for immediate and efficient transfer of patients to the nearest cardiac surgical facility that are reviewed/tested on a regular (quarterly) basis.
- Primary PCI must be performed routinely as the treatment of choice around the clock for a large proportion of patients with STEMI to ensure streamlined care paths with increased case volumes.
- Case selection for the performance of primary PCI must be rigorous. Criteria for the types of lesions appropriate for primary PCI and for the selection for transfer for emergent aortocoronary bypass surgery are shown in Table 11–5.
- There must be an ongoing program of outcomes analysis and formalized periodic case review.

Institutions should participate in a 3- to 6-month period of implementation during which time development of a formalized primary PCI program is instituted that includes establishing standards, training staff, detailed logistic development, and creation of a quality assessment and error management system.

IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

second hospital should be as short as possible, with a goal within 90 minutes. This goal is possible in the United States,[108] but remains unusual.[76] Directly transporting patients to PCI centers rather than transporting them to the nearest hospital may be a superior strategy to decrease time-to-treatment for primary PCI.

Table 11–5 Patient Selection for Primary PCI and Emergent Aortocoronary Bypass at Hospitals Without On-Site Cardiac Surgery

Avoid Intervention in Hemodynamically Stable Patients with

- Significant (≥60%) stenosis of an unprotected left main coronary artery upstream from an acute occlusion in the left coronary system that might be disrupted by the angioplasty catheter
- Extremely long or angulated infarct-related lesions with TIMI grade 3 flow
- Infarct-related lesions with TIMI grade 3 flow in stable patients with three-vessel disease
- Infarct-related lesions of small or secondary vessels
- Hemodynamically significant lesions in other than the infarct artery

Transfer Patients for Emergency Aortocoronary Bypass Surgery

- After primary PCI of occluded vessels if high-grade residual left main or multivessel coronary disease with clinical or hemodynamic instability is present (preferably with intraaortic balloon pump support)

IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction. Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

The Early Invasive Strategy

Routine cardiac catheterization and subsequent revascularization for suitable anatomy is now recommended for patients with NSTEMI.[109] Routine PCI performed within days after failed fibrinolysis has been evaluated in small studies, but there are no convincing data showing benefit.[110] The Occluded Artery Trial is evaluating whether routine PCI improves clinical outcomes in asymptomatic high-risk patients with an occluded infarct artery after occurrence of STEMI.[111] Older trials have also failed to demonstrate benefit for routine PCI hours to days after successful fibrinolysis.[112] However, improved equipment, improved antiplatelet and anticoagulant strategies, and the use of coronary stents have increased PCI success rates and decreased complications in the modern interventional cardiology era. Several reports now support this protocol, which has been referred to as a pharmacoinvasive strategy (see Fig. 11–7B).[113-116] Cardiac catheterization and revascularization for suitable anatomy should be performed in patients with spontaneous or provokable ischemia.[117]

HOSPITAL MANAGEMENT

Location

Patients should be admitted to the coronary care unit (CCU) when initial patient evaluation includes assessment of vital

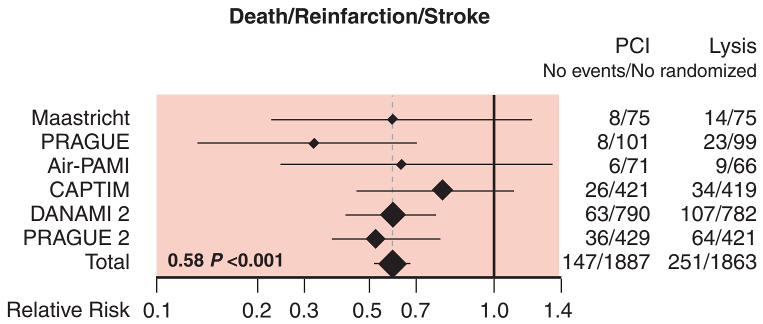


Figure 11–12 Relative risks for the composite of death, reinfarction, and stroke in 6 trials comparing transfer for primary PCI with immediate fibrinolysis for STEMI. (Adapted from Dalby M, Bouzamondo A, Lechat P, Montalescot G: Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: A meta-analysis. Circulation 2003;108:1809-14, with permission.)

signs, pulse oximetry, cardiac rhythm and ST-segments, and symptoms of acute cardiac ischemia. Outstanding (and abnormal) laboratory results should be followed up, and standard admitting orders to the CCU should be implemented (Table 11–6). Intra-arterial and pulmonary artery pressure monitoring should be available for severely hypotensive patients. The intra-aortic balloon pump should be available for treatment of cardiogenic shock. Aspirin and β-blocker therapy in an adequate dose to control heart rate should be administered. Intravenous nitroglycerin is useful for control of angina, hypertension, or acute heart failure. Oxygen can be discontinued after 6 hours of patient stability if the oxygen saturation is >90%.

Nursing care should be provided by individuals certified in critical care with staffing based on the specific needs of patients and provider competencies, as well as organizational priorities. Patients should be monitored for the development of heart failure, serious arrhythmias, or recurrent ischemia. Medications such as stool softeners or anti-anxiety agents should be given based on nursing judgment. Terminal patients (no-code) or patients whose comorbidities make survival unlikely should not be admitted to the CCU.

Patients should be transferred to a monitored bed in a stepdown unit after 12 to 24 hours of clinical stability. Similarly, low-risk patients who have undergone successful PCI can be directly admitted to the stepdown unit for post-PCI care rather than to the CCU. Pulse oximetry, electrocardiographic monitoring, and defibrillation equipment should be available. The nursing staff should have a skill set similar to CCU nurses so that they may evaluate and respond to any clinical complications.

Routine Measures

Bed rest should be limited to 12 to 24 hours because of the concern about physical deconditioning and orthostatic hypotension. Patients should have no oral intake before a procedure, but otherwise should be prescribed the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes (TLC) diet focusing on the following: reduced intake of fats and cholesterol, <7% of total calories as saturated fats, <200 mg/day of cholesterol, increased consumption of omega-3 fatty acids, and appropriate caloric intake for energy needs.[7] Diabetic patients need an appropriate diet, and sodium intake should be restricted in patients with hypertension or heart failure. Patient counseling regarding risk factor modification that includes smoking cessation, medication compliance, diet, and exercise should be part of every patient encounter.

It is reasonable to use anxiolytic medications to alleviate short-term anxiety. Withdrawal of caffeine is associated with headache and increases in heart rate. One to two cups of coffee a day, enough to avert caffeine withdrawal, has not been associated with blood pressure increases or ventricular arrhythmias. Smokers may experience symptoms of nicotine withdrawal including anxiety, insomnia, depression, difficulty concentrating, irritability, anger, restlessness, and slowed heart rate. Anxiolytics, bupropion, and nicotine replacement therapy are treatment options. Intravenous haloperidol is a rapidly-acting neuroleptic that can be given to cardiac patients with agitation. Communication with the patient and family, liberalized visiting rules, psychological support, and counseling can decrease anxiety and depression for both the patient and the family members.

Medications

Nitroglycerin

Intravenous nitroglycerin is indicated in the first 48 hours after STEMI for treatment of persistent ischemia that responds to nitrate therapy, CHF, or hypertension. Intravenous, oral, or topical nitrates are useful beyond the first 48 hours after STEMI for treatment of recurrent angina or persistent CHF if their use does not preclude therapy with β-blockers or ACE inhibitors. The continued use of nitrate therapy beyond the first 24 to 48 hours in the absence of symptoms is not well established in contemporary practice. If sustained nitrate therapy is planned, a nitrate-free interval during daily dosing is important to avoid nitrate tolerance (see Chapter 5).

Antithrombotic Agents

Aspirin should be continued indefinitely, unless aspirin allergy exists.[36] Lower aspirin doses of 75 to 162 mg are preferred for long-term treatment because of a dose-dependent increase of bleeding risk. A thienopyridine should be substituted for aspirin when aspirin is contraindicated because of hypersensitivity or major gastrointestinal intolerance (see Chapter 5). Gastric side effects may be reduced by administration of H_2 antagonists, antacids, or use of enteric-coated aspirin. Available data suggest that dual antiplatelet therapy with both aspirin and clopidogrel should be continued for at least 1 month in all patients.[38,39] Clopidogrel 75 mg daily is generally preferred to ticlopidine 250 mg twice daily because of clopidogrel's fewer side effects and once daily dosing.

Intravenous UFH or LMWH should be used in most patients for at least 48 hours or longer if the clinical condition

Table 11–6 Sample Admitting Orders for the Patient with STEMI

Condition: Serious
IV: NS or D_5W to keep vein open. Start a second IV if IV medication is being given. This may be a heparin lock.
Vital signs: Every 30 min until stable, then every 4 h as needed. Notify physician if HR is <60 bpm or >100 bpm, systolic BP is <100 mm Hg or >150 mm Hg, respiratory rate is <8 breaths per minute or >22 breaths per minute.
Monitor: Continuous ECG monitoring for arrhythmia and ST-segment deviation.
Diet: NPO except for sips of water until stable. Then start 2 g sodium/d, low saturated fat (<7% of total calories/day), low cholesterol (<200 mg/day) diet, such as Therapeutic Lifestyle Changes (TLC) diet.
Activity: Bed rest and bedside commode and light activity when stable.
Oxygen: Continuous oximetry monitoring. Nasal cannula at 2 L/min. When stable for 6 h, discontinue oxygen and assess for oxygen need (i.e., O_2 saturation of <90%), and consider discontinuing oxygen.
Medications:
Nitroglycerin
- Use sublingual NTG 0.4 mg every 5 minutes as needed for chest discomfort.
- Intravenous NTG for CHF, hypertension, or persistent ischemia.

ASA
- If ASA not given in the ED, chew nonenteric-coated ASA† 162-325 mg.
- If ASA has been given, start daily maintenance of 75-162 mg. May use enteric-coated ASA for gastrointestinal protection.

β-Blocker
- If not given in the ED, assess for contraindications, i.e., bradycardia and hypotension. Continue daily assessment to ascertain eligibility for β-blocker.
- If given in the ED, continue daily dose and optimize as dictated by HR and BP.

ACE Inhibitor
- Start ACE inhibitor orally in patients with anterior infarction, pulmonary congestion, or LVEF <0.40 if the following are absent: hypotension (SBP < 100 mm Hg or <30 mm Hg below baseline) or known contraindications to this class of medications.

Angiotensin-Receptor Blocker
- Start ARB orally in patients who are intolerant of ACE inhibitors and who have either clinical or radiologic signs of heart failure or LVEF < 0.40.

Pain Meds
- IV morphine sulfate 2-4 mg with increments of 2-8 mg IV at 5-15-min intervals as needed to control pain

Anxiolytics (based on a nursing assessment)
Daily Stool Softener
Laboratory Tests
- Serum biomarkers for cardiac damage,* CBC with platelet count, INR, aPTT, electrolytes, magnesium, BUN, creatinine, glucose, serum lipids

*Do not wait for results before implementing reperfusion strategy.
†Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with nonenteric-coated formulations.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; aPTT, activated partial thromboplastin time; BP, blood pressure; bpm, beats per minute; BUN, blood urea nitrogen; CBC, complete blood count; CHF, congestive heart failure; ECG, electrocardiogram; ED, emergency department; h, hours; HR, heart rate; INR, international normalized ratio; IV, intravenous; LVEF, left ventricular ejection fraction; min, minutes; NS, normal saline; NPO, nothing by mouth; NTG, nitroglycerin; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.
Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

necessitates prolonged bed rest or minimal activity. It is often discontinued earlier in patients treated with PCI so that the vascular sheaths can be removed. Deep venous thrombosis prophylaxis with subcutaneous LMWH (dosed appropriately for specific agent) or with subcutaneous UFH (7500 U to 12,500 U twice daily) until the patient is completely ambulatory may be useful, but the effectiveness of such a strategy is not well established in the contemporary era of routine aspirin use and early mobilization.

An aPTT measurement and dose adjustment should be made 3 hours after starting intravenous UFH therapy and repeated 6 hours after each dose adjustment and daily thereafter. Rather than abruptly stopping therapy, reducing UFH infusions in a gradual fashion (e.g., by one-half within 6 hours, then discontinuing over the subsequent 12 hours) may decrease the risk of hypercoagulability from heparin rebound. Platelet counts should be monitored daily because of the 3% risk of heparin-induced thrombocytopenia.

β-Blockers

A meta-analysis of trials from the prefibrinolytic era involving over 24,000 patients who received β-blockers in the convalescent phase has shown a reduction in acute ischemic events and

a 23% reduction in long-term mortality.[118] The risk is a 3% incidence of provocation of congestive heart failure or complete heart block and a 2% incidence of cardiogenic shock. β-Blockers are especially beneficial in patients with persistent or recurrent ischemia, evidence for infarct extension, or tachyarrhythmias. Initiation of therapy can be undertaken after 24 to 48 hours of freedom from relative contraindications that include bradycardia and congestive heart failure.

Inhibition of the Renin-Angiotensin-Aldosterone System

An ACE inhibitor should be administered orally during convalescence in patients who tolerate this class of medication. ACE inhibitors should not be used if systolic blood pressure is <100 mm Hg or <30 mm Hg below baseline; if clinically relevant renal failure is present; if there is a history of bilateral stenosis of the renal arteries; or if there is known allergy to ACE inhibitors. The proportional benefit of ACE inhibitor therapy is largest in higher risk subgroups; those patients with previous MI, heart failure, depressed LV ejection fraction (EF), or tachycardia. These patients should be given long-term therapy.[119-121] Survival benefit for the elderly and for low-risk subgroups is equivocal.[120,121] There are no data supporting therapy for longer than 4 to 6 weeks in patients without LV dysfunction. Treatment can be initiated with captopril 6.25 to 12.5 mg three times daily and titrated to 50 mg three times daily. If tolerated, a once daily ACE inhibitor can then be substituted.

An angiotensin receptor blocker should be administered to STEMI patients who are intolerant of ACE inhibitors and with either clinical or radiologic signs of heart failure or EF = 40%.[2] Valsartan (target dose 80 mg twice daily)[122] and candesartan (target dose 32 mg daily)[123] have demonstrated efficacy for this recommendation.

Long-term aldosterone blockade should be prescribed for patients without significant renal dysfunction (creatinine <2.5 mg/dL in men and <2.0 mg/dL in women) or hyperkalemia (potassium <5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF <40%, and have either symptomatic heart failure or diabetes.[2] The Randomized Aldactone Evaluation Study[124] treated patients with NYHA class III-IV heart failure with either spironolactone (25 to 50 mg daily) or placebo. Over 24 months of follow-up, spironolactone treatment was associated with an 11% absolute and a 24% relative risk reduction in all-cause mortality. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) randomized 6632 patients post-MI with an ejection fraction <40% and heart failure or diabetes to receive eplerenone (target dose 50 mg daily) or placebo in conjunction with routinely indicated cardiac medications.[125] There were significant reductions in overall mortality, cardiovascular mortality, and cardiac hospitalizations.

Glycemic Control

Metabolic modulation with infusions of glucose-insulin-potassium (GIK) was associated with mortality reduction in early trials. These results have not been reproduced in the reperfusion era with fibrinolytic therapy[126] or primary PCI.[127] The results may have been confounded by treatment after reperfusion rather than before reperfusion, later treatment, or treatment in low-risk patients. An excess risk has been reported for those in Killip class II or higher. Therapy with GIK cannot be recommended at the present time. However, compelling evidence for tight glucose control in critically ill patients supports the importance of intensive insulin therapy to achieve a normal blood glucose (80 to 110 mg/dL).[128,129]

Magnesium

Similar to the GIK story, early studies supported a mortality benefit with magnesium administration, but no benefit has been noted in contemporary trials.[31,130] Magnesium can be administered for repletion of documented electrolyte deficits and for life-threatening ventricular arrhythmias such as torsades de pointes.

Calcium Channel Blockers

It is reasonable to give verapamil or diltiazem to patients in whom β-blockers are ineffective or contraindicated (e.g., bronchospastic disease) for relief of ongoing ischemia or control of a rapid ventricular response with atrial fibrillation or flutter after STEMI in the absence of CHF, LV dysfunction, or AV block.[131,132] There are no current data, however, to suggest that these agents decrease cardiac events. Nifedipine (immediate-release) is generally contraindicated in the treatment of STEMI because of reflex sympathetic activation, tachycardia, and hypotension associated with its use.[133]

Hemodynamic Disturbances

Hemodynamic Assessment

Use of a pulmonary artery catheter to measure hemodynamics in patients developing progressive CHF or hypotension may permit the early diagnosis of a preshock state wherein aggressive pharmacologic support can prevent the onset of cardiogenic shock.[134] Before PCI is performed for cardiogenic shock, the interventional cardiologist should insert a pulmonary artery catheter to maximize the hemodynamic status of the patient and to diagnose unrecognized mechanical complications. After reperfusion therapy, the pulmonary artery catheter may be used to guide diuretic, inotropic, and vasopressor agents in hemodynamically unstable patients while the stunned myocardium is recovering. Although there are no randomized clinical trial data testing whether or not hemodynamic monitoring alters clinical outcome in STEMI, one would expect that revascularization of ischemic myocardium would be required for outcomes to be improved.

Complications of pulmonary artery catheterization include ventricular tachyarrhythmias (during manipulation), pulmonary hemorrhage or infarction, and transient right bundle branch block, which can lead to heart block in those with preexisting left bundle branch block. The catheter should not be inserted if the patient responds quickly to other interventions or if treatment is expected to be futile. The catheter should be expeditiously removed when it is no longer needed to monitor therapy or before 4 to 5 days owing to risk of infection.

Hypotension

Hypotension (systolic pressure <90 mm Hg or 30 points below previous mean arterial pressure) can result from hypovolemia, arrhythmias, RV or LV failure, mechanical complications of MI, or superimposed complications such as sepsis or pulmonary embolism. Hypovolemia is a common occurrence and may be due to inadequate intake, diaphoresis and vomiting, overdiuresis, excessive use of vasodilators, or inappropriate reflex peripheral vasodilation. Hemorrhage is an increasingly common problem associated with the use of invasive procedures, fibrinolytics, antiplatelet agents, and anticoagulant agents. Therefore, rapid volume loading is recommended as an initial therapeutic strategy for all patients without clinical evidence for volume overload (Fig. 11–13). Persistent hypotension should be evaluated with an echocardiogram to define the cardiac anatomy and with a hemoglobin measurement. Correction or control of rhythm disturbances or conduction abnormalities often reverses hypotension. In patients with inotropic failure, vasopressors and inotropic agents are

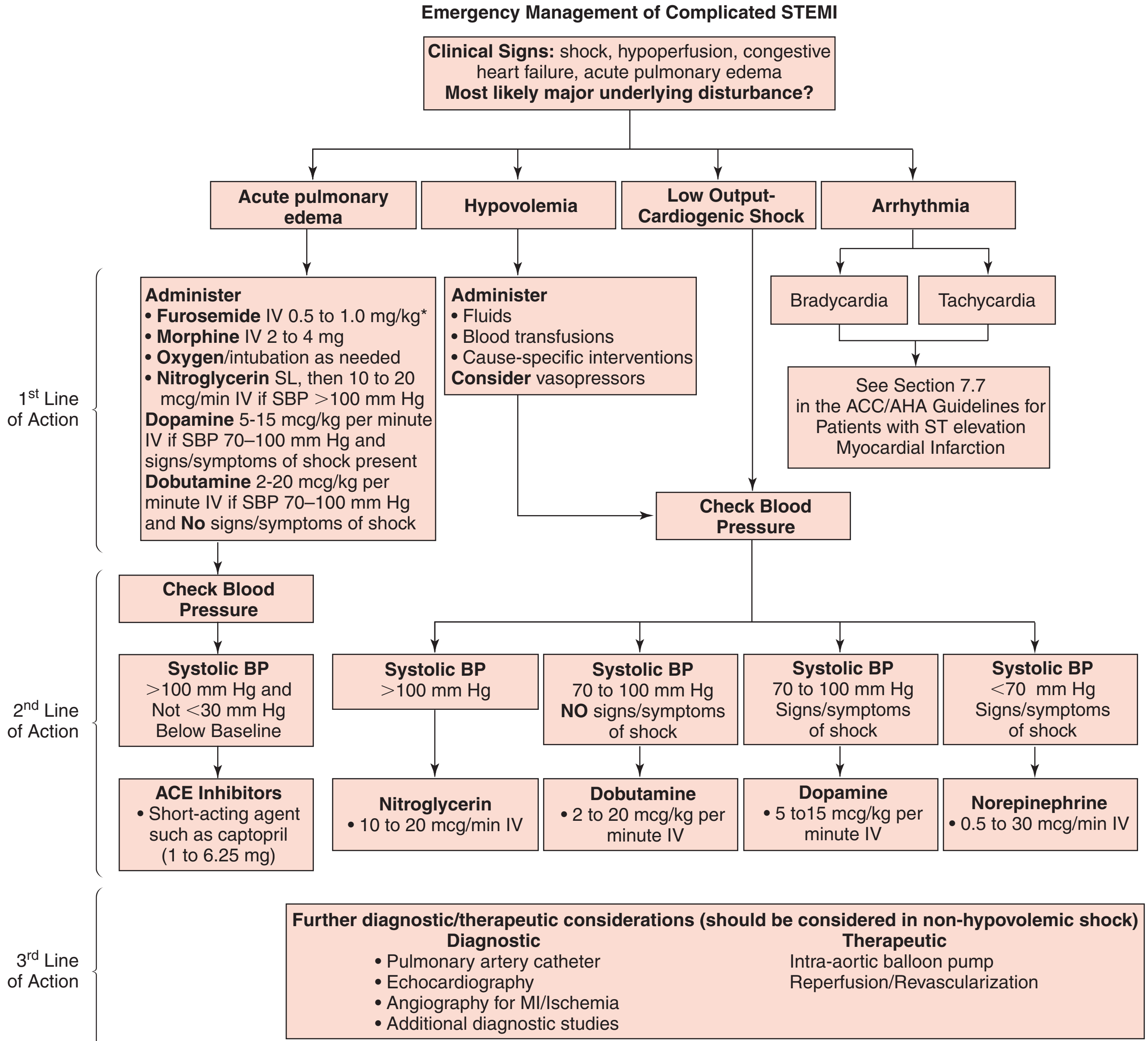


Figure 11–13 Emergency management of complicated ST-elevation myocardial infarction (STEMI). The emergency management of patients with cardiogenic shock, acute pulmonary edema, or both, is shown. *Furosemide <0.5 mg/kg for new onset acute pulmonary edema without hypovolemia; 1 mg/kg for acute or chronic volume overload, renal insufficiency. Nesiritide has not been studied adequately in patients with STEMI. Combinations of medications (e.g., dobutamine and dopamine) may be used. ACE, angiotensin-converting enzyme; BP, blood pressure; IV, intravenous; MI, myocardial infarction; SBP, systolic blood pressure; SL, sublingual. (Adapted from ECC Guidelines: Part 7: The Era of Reperfusion; Section 1: Acute Coronary Syndromes [Acute Myocardial Infarction]. 2000 American Heart Association, Inc. Circulation 2000;102: I-172-203.)

required. Dopamine is the agent of first choice, but norepinephrine may be required for marked hypotension. Once arterial pressure is brought to at least 90 mm Hg, intravenous dobutamine may be given simultaneously in an attempt to reduce the rate of the dopamine infusion. In addition, consideration should be given to initiating intra-aortic balloon pump (IABP) counterpulsation.

Low-Output State

A preshock state of hypoperfusion with normal blood pressure may develop before circulatory collapse and is manifested by cold extremities, cyanosis, oliguria, or decreased mentation.[134] Hospital mortality is high, so these patients should be aggressively diagnosed and treated as if they had cardiogenic shock (see Fig. 11–13). Dobutamine infusion is the initial pharmacologic intervention. IABP therapy may be required to improve coronary artery perfusion pressure if hypotension is present. If the blood pressure permits, afterload reducing agents should be added to decrease cardiac work and pulmonary congestion. Coronary artery revascularization of ischemic myocardium with either PCI or CABG has been shown to decrease mortality in patients with cardiogenic shock and is strongly recommended for suitable candidates.[69,135] Likewise, patients with ventricular septal rupture, papillary muscle rupture, or pericardial tamponade may benefit from emergency surgical repair.

Pulmonary Congestion

LV filling pressures may rise rapidly after acute coronary occlusion. This leads to rapid redistribution of fluid from the intravascular space into the lung interstitium and alveoli. The etiology of pulmonary edema (systolic, diastolic or a mechanical complication [mitral regurgitation or ventricular septal rupture]) should be rapidly assessed with a 2-dimensional echocardiogram with color flow Doppler. Pulmonary congestion increases the risks of death and pulmonary edema and is associated with a 20% to 40% 30-day mortality rate even in the fibrinolytic era.[136,137]

Oxygen supplementation should be administered to maintain the arterial saturation >90%. Management includes the use of agents that acutely reduce preload: nitrates, morphine sulfate, and diuretics (see Fig. 11–13), and avoidance of acute administration of negative inotropic agents (e.g., β-blockers and calcium channel antagonists). A 10-to 20-mcg nitroglycerin bolus should be administered, followed by 10 mcg/min infusion, increased by 5 to 10 mcg/min every 5 to 10 minutes until dyspnea is relieved, the mean arterial pressure is lowered by 10% in normotensive patients or by 30% in hypertensive patients, or until the heart rate increases by more than 10 beats per minute. Loop diuretics (furosemide, torsemide, or bumetanide) should be initiated in low-to-intermediate doses in patients with associated hypervolemia.

Oral ACE inhibitors, preferably a short-acting agent such as captopril, beginning with 1 to 6.25 mg, should be instituted early in normotensive or hypertensive patients. The dosage may be doubled with each subsequent dose, as tolerated, up to 25 to 50 mg every 8 hours, then changed to a long-acting agent. For patients who presented with CHF complicating MI, ramipril administration between days 3 and 10 significantly reduces 30-day mortality.[138] ACE inhibitors are the only adjunctive medication (beyond ASA and reperfusion therapy) shown to reduce 30-day mortality when CHF complicates STEMI, so ACE inhibitors are preferred if blood pressure limits use of vasodilators. Intravenous sodium nitroprusside substantially reduces afterload as well as preload; however, its use has been associated with coronary steal. Digitalis has no role in the management of pulmonary edema that complicates STEMI unless rapid atrial fibrillation is present.

Eplerenone, an aldosterone antagonist, prevented death and recurrent hospitalization in patients 3 to 14 days post-MI with congestive heart failure and LVEF <0.40.[125] Spironolactone improved survival in a population of patients with chronic CHF, which includes those with remote MI[124] and is generic. In contrast to the recommendation to avoid β-blockade during pulmonary edema, β-blockers are strongly recommended before hospital discharge for secondary prevention of cardiac events.[139] The initial dose and titration should be based on clinical heart failure status and LVEF.

Mechanical ventilation may be required. It may be reasonable to insert an IABP when pulmonary congestion is refractory. Analyses from GUSTO IIb[140] and the NRMI registry[80] showed a marked benefit of PCI compared with fibrinolytic therapy for patients with CHF. Coronary angiography and revascularization, based on the anatomy, should be performed when late CHF complicates the hospital course.

Cardiogenic Shock

Fewer than 1% of patients with STEMI present to the hospital in cardiogenic shock, and approximately 7% develop shock after hospital admission. A useful definition of cardiogenic shock is clinical evidence of systemic hypoperfusion with systolic BP <90 mm Hg for at least 30 minutes (or the need for supportive measures to maintain systolic BP >90 mm Hg), cardiac index <2.2 liters per minute per square meter, and PCWP at least 15 mm Hg.

Cardiogenic shock is caused by extensive LV dysfunction in 75% of patients. Other causes include acute severe mitral regurgitation, ventricular septal rupture, subacute free wall rupture with tamponade, and RV infarction. Aortic dissection and hemorrhagic shock may mimic cardiogenic shock and need to be excluded in the differential diagnosis. Echocardiography with color flow Doppler should be used to define the etiology of shock.

Patients with cardiogenic shock secondary to myocardial ischemia and infarction should be resuscitated as quickly as possible. Restoration of sinus rhythm, adequate ventilation, correction of acid-base abnormalities, and inotropic and vasopressor therapy to support tissue perfusion are important interventions. They should be treated with reperfusion therapy, unless further care is deemed futile (Fig. 11–14). However, reperfusion rates with fibrinolytic therapy are reduced in cardiogenic shock because of low cardiac output, and it is not clear that survival rates are improved. In contrast, more than 20 observational studies have suggested that reperfusion with PCI or CABG improves survival rates.[137]

Two randomized trials have been performed. The SHOCK trial[69,135] randomized 302 patients to either emergency revascularization or initial medical stabilization. The 30-day mortality rate for emergency revascularization patients was 46.7% versus 56.0% for initial medical stabilization patients ($P = 0.11$). However, the mortality rate was significantly lower

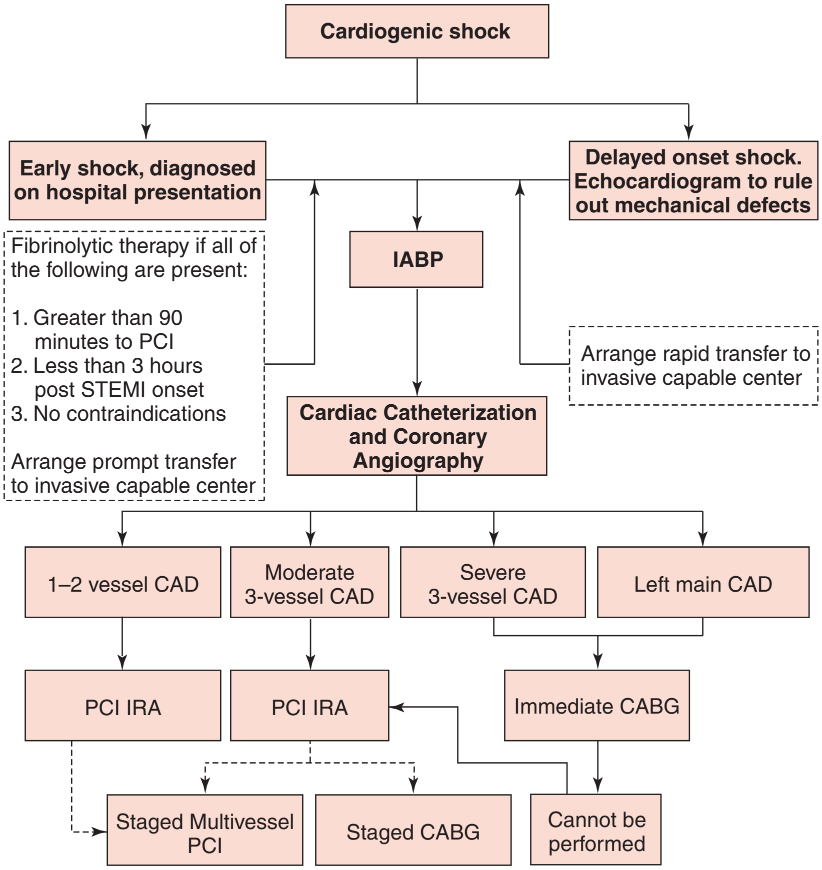


Figure 11–14 Recommendations for initial reperfusion therapy when cardiogenic shock complicates STEMI. Early mechanical revascularization with PCI/CABG is a class I recommendation for candidates <75 years of age with ST elevation or LBBB who develop shock <36 hours from STEMI and in whom revascularization can be performed within 18 hours of shock, and a class IIa recommendation for patients ≥75 years of age with the same criteria. Eighty-five percent of shock cases are diagnosed after initial therapy for STEMI, but most patients develop shock within 24 hours. An IABP is recommended when shock is not quickly reversed with pharmacologic therapy, as a stabilizing measure for patients who are candidates for further invasive care. *Dashed lines* indicate that the procedure should be performed in patients with specific indications only. CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; IABP, intra-aortic balloon pump; IRA, infarct-related artery; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. (Adapted from Hochman JS: Cardiogenic shock complicating acute myocardial infarction: Expanding the paradigm. Circulation 2003;107: 2998-3002, with permission.)

in the emergency revascularization group at 6 months (50.3% versus 63.1%, $P < 0.03$) and 12 months (53.3 % versus 66.4, $P < 0.03$). Similarly, the (S)MASH study ([Swiss] Multicenter Trial of Angioplasty for Shock) randomly assigned 55 refractory shock patients to either PCI or conventional care.[141] As in SHOCK, the mortality rate in the PCI group was 9 absolute percentage points lower at 30 days (69% versus 78%) than the conventional therapy group, but did not reach statistical significance because of sample size. The results of the SHOCK trial and registry and the SMASH trial have proved that appropriate candidates with cardiogenic shock complicating acute MI should be referred for coronary angiography and emergency revascularization unless contraindications exist. These include life-shortening illnesses, previously defined coronary anatomy unsuitable for revascularization, anoxic brain damage, and patients for whom further therapy appears to be futile.

Triple-vessel disease (60%) and left main disease (20%) are often present when shock complicates STEMI. Among the emergency revascularization groups in the SHOCK trial, 60% received PCI and 40% had CABG. The 30-day mortality rate was 45% and 42%, respectively, despite more severe CAD and twice the frequency of diabetes in patients treated with CABG. This was in contrast to the 69% in-hospital mortality rate reported for those with three-vessel CAD who underwent PCI. Although CABG will be an option for some patients, most will be treated with PCI of the infarct artery. Surviving patients with multivessel disease can subsequently be considered for additional PCI or CABG to achieve more complete revascularization.

The only subgroup of patients that did not receive a treatment benefit in the SHOCK trial was the 56 patients who were 75 years or older. However, analysis of the 44 elderly patients in the SHOCK Trial registry[142] selected for early revascularization showed a significantly lower mortality rate than that of the 233 patients who did not undergo revascularization (48% versus 81%; $P = 0.0002$). Other reports[143,144] also support the use of primary PCI in carefully selected older patients with cardiogenic shock complicating MI, so age alone should not be an exclusion criterion for selecting patients for cardiac catheterization.

Fibrinolytic therapy should be administered to those who are not candidates for early revascularization and who do not have contraindications for lytic therapy. Patients who present to hospitals without revascularization capability should be transferred to a hospital with revascularization capability. IABP placement prior to transport may help stabilize the patient. If the patient presents in shock within 3 to 6 hours of MI onset and delays in transport and intervention are anticipated, both fibrinolytic therapy and IABP counterpulsation may be initiated.[145]

Right Ventricular Infarction

RV ischemia can be demonstrated in up to one half of patients with inferior STEMI, although only 10% to 15% show the

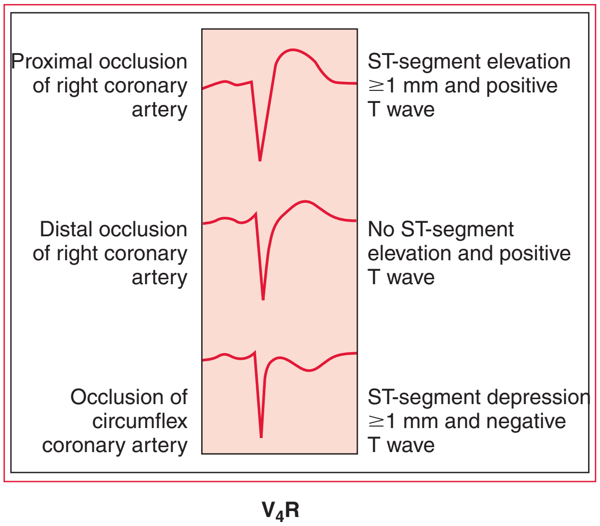
classic hemodynamic abnormalities of clinically significant RV infarction.[83,146] These patients represent a high-risk subgroup of patients with a 25% to 30% mortality rate.[147] In the SHOCK trial registry, patients with predominant RV infarction and cardiogenic shock had a mortality rate similar to patients with LV shock (53% versus 61%).[148]

The right coronary artery usually supplies most of the RV myocardium. Occlusion of this artery proximal to the RV branches will lead to RV ischemia. Most survivors demonstrate a return of normal RV function over a period of weeks to months, suggesting that RV stunning, rather than irreversible necrosis, has occurred. Pathophysiologic reasons for this phenomenon include lower oxygen demand because of lower myocardial mass than in the LV,[149] coronary perfusion during both diastole and systole,[150] and more favorable oxygen supply than in the LV because of more extensive collateral supply.[151]

The extent of RV dysfunction, the restraining effect of the surrounding pericardium, and interventricular dependence related to the shared interventricular septum determine the hemodynamic effect of RV ischemia. The ischemic RV dilates, increasing intrapericardial pressure because of the restraining forces of the pericardium. Consequently, there is a reduction in RV systolic pressure and output, decreased LV preload, a reduction in LV end-diastolic dimension and stroke volume, and a shifting of the interventricular septum toward the LV.[152] The pressure gradient between the right and left atria becomes an important driving force for pulmonary perfusion. Factors that reduce preload (volume depletion, diuretics, morphine, nitrates) or diminish augmented right atrial contraction (atrial infarction, loss of AV synchrony, atrial fibrillation), or factors that increase RV afterload (LV dysfunction), can have profound adverse hemodynamic effects.[153,154] Paradoxic interventricular septal motion that bulges in piston-like fashion into the RV, is important in generating systolic force, which improves pulmonary perfusion.[155] Concomitant septal infarction may result in the loss of this compensatory mechanism.

All patients with inferior STEMI should be evaluated for possible RV ischemia/infarction. The clinical triad of hypotension, clear lung fields, and elevated jugular venous pressure in the setting of IMI is specific, but has a sensitivity of <25%.[156] Distended neck veins alone or the presence of the Kussmaul sign (distention of the jugular vein on inspiration) are both sensitive and specific,[157] unless the patient is volume depleted. All patients with inferior STEMI should be screened for RVMI with right-sided ECG recordings at the time of admission (Fig. 11–15). Demonstration of 1-mm ST-segment elevation in the lead V_1 and in the right precordial lead V_4R is the most predictive electrocardiographic finding in patients with RV ischemia[158] but may resolve within 10 hours of onset of symptoms.[159] Echocardiography can show RV dilation and asynergy or abnormal interventricular and interatrial septal motion. Right-to-left shunting through a patent foramen ovale should be suspected when persistent hypoxia is not responsive to supplemental oxygen and can be documented with the color flow Doppler examination.[160] Pulmonary artery catheterization may be helpful in diagnosing RV ischemia/infarction. A right atrial pressure of 10 mm Hg or greater and >80% of pulmonary wedge pressure is a relatively sensitive and specific finding.

Successful reperfusion therapy can prevent or reverse the hemodynamic complications of RVMI. PCI is particularly useful in patients with hypotension or shock because RV ischemic dysfunction resolves quickly with successful reperfusion. The medical treatment of patients with RV ischemic dysfunction is different than, and often diametrically opposed to, management of LV dysfunction. The first goal is to maintain RV preload. Nitrates, morphine, and diuretics are routinely used in LVMI, but should be avoided in RVMI because they may reduce RV preload, cardiac output, and blood pressure. Volume loading with normal saline can improve cardiac output and blood pressure, but should not be excessive because RV dilatation shifts the interventricular septum into the LV, decreasing LV output.[161] The second goal is to provide inotropic support for the ischemic right ventricle with dobutamine hydrochloride. The third goal is to maintain AV synchrony. High-degree AV block may occur in as many as one half of these patients.[162] Atrioventricular sequential pacing may restore normal blood pressure when ventricular pacing alone has been unsuccessful.[163] Atrial fibrillation may occur in up to one third of patients and should be treated with cardioversion if hemodynamic compromise is present. The



Clinical findings:
Shock with clear lungs, elevated JVP, Kussmaul sign

Hemodynamics:
Increased RA pressure (y descent)
Square root sign in RV tracing

ECG:
ST elevation in R sided leads

Echo:
Depressed RV function

Management:
Maintain RV preload
Lower RV afterload (PA—PCW)
Restore AV Synchrony
Inotropic support
Reperfusion

Figure 11–15
Electrocardiographic tracings of right ventricular infarction. AV, atrioventricular; JVP, jugular venous pressure; PA, pulmonary artery; PCW, pulmonary capillary wedge; RA, right atrial; RV, right ventricular. (Adapted from Wellens HJ: The value of the right precordial leads of the electrocardiogram. N Engl J Med 1999;340:381-3, with permission.)

fourth goal is to decrease RV afterload in the setting of LV failure. This can be accomplished with afterload-reducing agents or intra-aortic balloon counterpulsation.

Mechanical Complications

Mitral Regurgitation

Patients with mild mitral regurgitation after STEMI have a worse prognosis than patients without mitral regurgitation.[164] Severe mitral regurgitation may be due to either posterior papillary muscle infarction, ischemia, or marked LV dilatation secondary to extensive infarction and remodeling (Table 11–7). Initial management should include afterload reduction and possible IABP. If the mitral regurgitation does not improve over several days or if surgery is required because of critical coronary anatomy or ongoing ischemia, a transesophageal echocardiogram should be performed to help determine whether valve replacement or annuloplasty is indicated. Mitral valve surgery, usually annuloplasty, should be performed at the same time as CABG for patients with moderate ischemic mitral regurgitation.[165]

The presence of pulmonary edema or cardiogenic shock suggests the possibility of acute papillary muscle rupture. If acute papillary muscle rupture is confirmed by echocardiography, urgent surgery should be pursued because delay increases the risk of further myocardial injury, other organ injury, and death.[166] These patients should be stabilized with afterload reduction, inotropic support, and an IABP, and should undergo coronary angiography before surgery. In the SHOCK Trial Registry,[167] 8% of patients with shock presented with severe MR and had an overall hospital mortality rate of 55%. Mortality with medical treatment was 71% compared with 40% treated with surgery.

Table 11–7 Characteristics of Ventricular Septal Rupture, Rupture of the Ventricular Free Wall, and Papillary-Muscle Rupture

Characteristic	Ventricular Septal Rupture	Rupture of Ventricular Free Wall	Papillary-Muscle Rupture
Incidence	1-3% without reperfusion therapy, 0.2-0.34% with fibrinolytic therapy, 3.9% among patients with cardiogenic shock	0.8-6.2%. Fibrinolytic therapy does not reduce risk; primary PTCA seems to reduce risk	About 1% (posteromedial more frequent than anterolateral papillary muscle)
Time course	Bimodal peak; within 24 hours and 3-5 days; range 1-14 days	Bimodal peak; within 24 hours and 3-5 days; range 1-14 days	Bimodal peak; within 24 hours and 3-5 days; range 1-14 days
Clinical manifestations	Chest pain, shortness of breath, hypotension	Anginal, pleuritic, or pericardial chest pain, syncope, hypotension, arrhythmia, nausea, restlessness, hypotension, sudden death	Abrupt onset of shortness of breath and pulmonary edema; hypotension
Physical findings	Harsh holosystolic murmur, thrill (+), S_3, accentuated 2nd heart sound, pulmonary edema, RV and LV failure, cardiogenic shock	Jugulovenous distention (29% of patients), pulsus paradoxus (47%), electromechanical dissociation, cardiogenic shock	A soft murmur in some cases, no thrill, varying signs of RV overload, severe pulmonary edema, cardiogenic shock
Echocardiographic findings	Ventricular septal rupture, left-to-right shunt on color flow Doppler echocardiography through the ventricular septum, pattern of RV overload	>5 mm pericardial effusion not visualized in all cases, layered, high-acoustic echoes within the pericardium (blood clot), direct visualization of tear, signs of tamponade	Hyper-contractile LV, torn papillary muscle or chordae tendineae, flail leaflet, severe mitral regurgitation on color flow Doppler echocardiography
Right-heart catheterization	Increase in oxygen saturation from the RA to RV, large V waves*	Ventriculography insensitive, classic signs of tamponade not always present (equalization of diastolic pressures among the cardiac chambers)	No increase in oxygen saturation from the RA to RV, large V waves*, very high pulmonary capillary wedge pressures

*Large V waves are from the pulmonary capillary wedge pressure.
LV, left ventricle; PTCA, percutaneous transluminal coronary angioplasty; RA, right atrium; RV, right ventricle.
Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

Ventricular Septal Rupture

The diagnosis of ventricular septal rupture can be confirmed by color flow Doppler echocardiography or by a step-up in oxygen saturation from the right atrium to the pulmonary artery (see Table 11–7). Similar to acute severe mitral regurgitation, management includes inotropic and vasodilator therapy, intra-aortic balloon counterpulsation, and immediate surgical repair. The usual operation involves excision of all necrotic tissue, patch repair of the septal rupture, and CABG. In the GUSTO-1 trial,[168] the mortality rates for surgical or medically treated patients with ventricular septal rupture were 47% and 94%, respectively. In patients with cardiogenic shock enrolled in the SHOCK registry,[169] mortality rates for surgical or medically treated patients were 81% and 96%, respectively. Therefore, if possible, hemodynamically stable patients should undergo emergency surgery before the onset of shock.

Left Ventricular Free Wall Rupture

Cardiac rupture occurs in 1% to 6% of patients and accounts for 15% of in-hospital mortality (see Table 11–7).[170] Early reperfusion and the presence of collateral circulation decrease the risk of free wall rupture. Risk factors include advanced age, female gender, first infarction, large infarction, and delivery of fibrinolytic therapy more than 14 hours after onset of symptoms.[170,171] Many patients die rapidly with irreversible electromechanical dissociation, but others develop hypotension and pericardial tamponade. The diagnosis of tamponade or pseudoaneurysm can be made quickly by echocardiography. Rapid volume administration and transfer to the operating room without cardiac catheterization for emergency surgery is recommended. The surgical mortality rate is approximately 60%.[172,173]

Left Ventricular Aneurysm

Ventricular aneurysm formation usually occurs in association with left anterior descending artery occlusion and a wide area of infarction. Clinical complications include angina pectoris, CHF, thromboembolism, and ventricular arrhythmias. Successful reperfusion therapy decreases the risk of aneurysm formation. Surgery is rarely required for control of heart failure or intractable ventricular arrhythmias unresponsive to conventional therapy. Surgical techniques include plication, excision with linear repair, and ventricular reconstruction using endoventricular patches to maintain better physiologic function.[174] Left ventricular size and function determine prognosis. Surgical mortality is 3% to 7%.

Mechanical Support Devices

IABP counterpulsation improves diastolic coronary blood flow and reduces myocardial work by afterload reduction. It should be used in patients with hypotension (systolic blood pressure <90 mm Hg or 30 points below previous mean arterial pressure) who do not respond to other interventions, low output syndrome, or cardiogenic shock. It also is useful for patients with recurrent ischemic-type chest discomfort and signs of hemodynamic instability, poor LV function, or a large area of myocardium at risk to stabilize them for cardiac catheterization and possible revascularization. Intra-aortic balloon counterpulsation may also be a reasonable intervention in the management of refractory polymorphic ventricular tachycardia or refractory congestive heart failure. Other support devices that are rarely used because of the comorbidities in these patients are left ventricular assist devices and extracorporeal membrane oxygenation. Survivors may become elective cardiac transplantation candidates.

Arrhythmias

Bradyarrhythmias

Bradyarrhythmias may be due to overstimulation of vagal afferent receptors and resulting cholinergic stimulation or to ischemic injury of conducting tissue. Sinus bradycardia is frequent, especially in the first hours of inferior STEMI, with reperfusion of the right coronary artery (Bezold-Jarisch reflex), or after the use of β-blocker or calcium antagonist medications (see Chapter 5). Intraventricular conduction delay has been reported in 10% to 20% of patients and heart block may develop in 6% to 14% of patients (Table 11–8). Both are associated with an increased mortality risk because they are generally related to a larger ischemia/infarct zone.[22]

Symptomatic Mobitz I AV block, symptomatic sinus bradycardia, sinus pauses >3 seconds, and sinus bradycardia with a heart rate <40 beats per minute associated with hypotension or signs of systemic hemodynamic compromise should be treated with an intravenous bolus of atropine 0.6 to 1.0 mg. Isoproterenol and aminophylline are not recommended because they are arrhythmogenic and increase myocardial oxygen demand. Glucagon has been used to treat bradycardia caused by toxic doses of β-blockers and calcium channel blockers.[175] If bradycardia is persistent, and maximal (2 mg) doses of atropine have been used, transcutaneous or transvenous temporary pacing should be instituted. When there is infranodal AV block, atropine may increase the sinus rate without affecting infranodal conduction, and so the effective ratio of conduction may decrease, and ventricular rate may decrease. Therefore, temporary pacing should be used instead of pharmacologic therapy.

Ventricular asystole may be caused either by failure of the sinus node to generate a cardiac impulse or by the development of complete heart block, with concurrent failure of the usual underlying atrial, junctional, or ventricular escape mechanisms. Treatment of the acute event requires prompt institution of chest compressions, atropine, vasopressin (40 IU), epinephrine, and transcutaneous pacing. It is important to address the underlying cause and discontinue medications that suppress electrical activity.

The decision to implant a permanent pacemaker for sinus node dysfunction or Mobitz I second-degree AV block should be delayed several days because the conduction abnormality usually resolves and does not affect long-term prognosis.[176] Permanent ventricular pacing is indicated for persistent second-degree or third-degree AV block or transient second- or third-degree infranodal AV block associated with bilateral bundle branch block. Patients who have permanent atrial fibrillation or flutter should receive a ventricular-pacing system. Patients who are in sinus rhythm should receive a permanent dual chamber pacemaker. Patients with heart failure may be candidates for resynchronization therapy with

Table 11–8 Features of Atrioventricular Conduction Disturbances in Acute Myocardial Infarction

	Location of AV Conduction Disturbance	
Feature	Proximal	Distal
Site of block	Intranodal	Infranodal
Site of infarction	Inferoposterior	Anteroseptal
Compromised arterial supply	RCA (90%), LCx (10%)	Septal perforators of LAD
Pathogenesis	Ischemia, necrosis, hydropic cell swelling, excess parasympathetic activity	Ischemia, necrosis, hydropic cell swelling
Predominant type of AV nodal block	First degree (PR > 200 msec) Mobitz type I second degree	Mobitz type II second degree Third degree
Common promontory features of third-degree AV block	First-second degree Mobitz type I pattern	
Features of escape following third-degree block		
• Location	• Proximal conduction system (His bundle)	• Distal conduction system (bundle branches)
• QRS width	• <0.12 sec*	• >0.12 sec*
• Rate	• 45-60 per min but may be as low as 30 per min	• Often <30 per min
• Stability of escape rhythm	• Rate usually stable; asystole uncommon	• Rate often unstable with moderate-to-high risk of ventricular asystole
Duration of high-grade AV block	Usually transient (2-3 days)	Usually transient, but some form of AV conduction disturbances and/or intraventricular defect may persist
Associated mortality rate	Low unless associated with hypotension and/or congestive heart failure	High because of extensive infarction associated with power failure or ventricular arrhythmias
Pacemaker therapy		
• Temporary	• Rarely required; may be considered for bradycardia associated with left ventricular power failure, syncope, or angina	• Indicated in patients with anteroseptal infarction and acute bifascicular block
• Permanent	• Almost never indicated; because conduction defect is usually transient	• Indicated for patients with high-grade AV block with block in His-Purkinje systems and those with transient advanced AV block and associated bundle branch block

*Some studies suggest that a wide QRS escape rhythm (>0.12 sec) after high-grade AV block in inferior infarction is associated with a worse prognosis.
AV, atrioventricular; RCA, right coronary artery; LCx, left circumflex artery; LAD, left anterior descending artery.
Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

biventricular pacing. Patients who have severe left ventricular dysfunction and an indication for permanent pacing should be evaluated for implantable cardioverter-defibrillator (ICD) indications.

Supraventricular Arrhythmia

Atrial fibrillation can occur in as many as 20% of patients in high-risk subgroups. Precipitating factors for atrial fibrillation and atrial flutter include excessive sympathetic stimulation, atrial stretch due to LV or RV dysfunction, atrial infarction due to circumflex or right coronary lesions, pericarditis, hypokalemia, underlying chronic lung disease, and hypoxia. Atrial fibrillation predicts a worse in-hospital and long-term outcome.[177,178] Systemic embolization is more frequent in patients with paroxysmal atrial fibrillation (1.7%) compared with those without (0.6%), with one half of embolic events occurring on the first day of hospitalization and more than 90% occurring by the fourth day.[179] Patients with atrial fibrillation or atrial flutter need to be considered for cardioversion, rate control, and anticoagulation therapy.

Synchronized cardioversion should be performed if the patient has persistent ischemic pain or is unstable because of tachycardia, hypotension, or heart failure. Brief general anesthesia or conscious sedation should precede an initial monophasic shock of 200 J for atrial fibrillation and 50 J for

atrial flutter. Successive shocks, if required, should increase in increments of 100 J. The interval between two consecutive shocks should not be <1 minute to avoid myocardial damage.[180]

Rate control can be achieved with intravenous β-blocker therapy, intravenous diltiazem (20 mg [0.25 mg/kg]) over two minutes followed by an infusion of 10 mg/hour, or intravenous verapamil (2.5 to 10 mg over 2 minutes; may repeat after 15 to 30 minutes). If these agents are contraindicated because of CHF or severe pulmonary disease, amiodarone is effective and well tolerated. If anticoagulation is required, either UFH or LMWH may be used.

Reentrant paroxysmal supraventricular tachycardia, because of its rapid rate, should be treated with the following in sequence: carotid sinus massage, intravenous adenosine (6 mg × 1 over 1 to 2 seconds; if no response, 12 mg over 1 to 2 seconds), intravenous β-adrenergic blockade, intravenous diltiazem, and intravenous digoxin. Both paroxysmal supraventricular tachycardia and atrial flutter can be terminated with atrial pacing.

Ventricular Arrhythmias

The mechanisms for ventricular tachyarrhythmias include loss of transmembrane resting potential, reentrant mechanisms due to dispersion of refractoriness in the border zones between infarcted and nonischemic tissues, and the development of foci of enhanced automaticity. Reperfusion arrhythmias appear to involve washout of toxic metabolites and of various ions such as lactate and potassium. Important contributing factors include heightened adrenergic tone, hypokalemia, hypomagnesemia, intracellular hypercalcemia, acidosis, free fatty acid production from lipolysis, and free radical production from reperfusion of ischemic myocardium.

Treatment of isolated ventricular premature beats, couplets, nonsustained ventricular tachycardia (VT), and accelerated idioventricular rhythm is not indicated. Electrolytes and pH should be normalized. The majority of episodes of VT and VF after STEMI occur within the first 48 hours.[181] Sustained VT or VF that occurs more than 48 hours after STEMI may denote an arrhythmic substrate that deserves further evaluation by electrophysiology testing.

Immediate cardioversion is generally not needed for sustained VT rates <150 beats per minute unless hemodynamic compromise is present. Sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure <90 mm Hg) should be treated with amiodarone 150 mg infused over 10 minutes (alternative dose 5 mg/kg) and repeated 150 mg every 10 to 15 minutes as needed. An alternative infusion is 360 mg over 6 hours (1 mg/min), then 540 mg over the next 18 hours (0.5 mg/min). The total cumulative dose, including additional doses given during cardiac arrest, must not exceed 2.2 g over 24 hours. A procainamide bolus and infusion is another option. Synchronized electrical cardioversion starting at monophasic energies of 50 J can also be performed. Sustained VT (more than 30 seconds or causing hemodynamic collapse) should be treated immediately with a synchronized electrical shock of 100 J. Increasing energies may be used if the initial shock is not successful.

Sustained polymorphic VT should be considered in a similar fashion to VF and managed with an unsynchronized electrical shock starting at 200 J. Uncontrolled ischemia and increased sympathetic tone are best treated by intravenous β-blockade, IABP, or emergency revascularization. Intravenous magnesium may be needed to increase serum magnesium to >2.0 mg/dL, and serum potassium should be >4.0 mEq/dL. If the patient has a heart rate of <60 beats per minute or a long QTc interval, temporary pacing at a higher rate may be instituted.

Primary VF is more prevalent in patients aged >75 years[182] and the incidence is highest (3% to 5%) in the first 4 hours of STEMI.[181] Current early therapeutic interventions appear to have decreased the incidence of primary VF[183] and the case fatality rate appears to be declining.[184] Primary VF increases hospital mortality but not long-term prognosis in survivors.[185] Current data do not support prophylactic antiarrhythmic therapy.[186,187] However, intravenous β-blockade and normalization of potassium and magnesium levels may decrease the risk of primary VF.[188] Ventricular fibrillation or pulseless VT should be treated with an unsynchronized electrical shock with an initial monophasic shock energy of 200 J, progressing to 300 J, and 360 J, if necessary. For patients with VF not easily converted by defibrillation, vasopressin 40 U intravenous push may be substituted for epinephrine 1 mg.[189] VF or pulseless VT that is refractory to electrical shock can be treated with amiodarone (300 mg or 5 mg/kg, IV bolus) followed by a repeat unsynchronized electrical shock.

An ICD is indicated for patients with VF or sustained VT more than 48 hours after STEMI (Fig. 11–16).[190-192] Prophylactic ICD implantation is also indicated for patients with a reduced left ventricular ejection fraction at least 1 month after STEMI.[193-195,195a]

Recurrent Chest Pain

Recurrent Ischemia/Infarction

Chest pain similar to the initial ischemic-type chest discomfort can occur at rest or with limited activity during hospitalization. This may or may not be associated with reelevation of the CK-MB, ST segment depression or elevation, or pseudonormalization of inverted T waves. Reinfarction occurs in 4% to 5% of patients after fibrinolytic therapy and aspirin. Diagnosis should be based on recurrence of severe ischemic-type chest discomfort that lasts at least 30 minutes, recurrent ST-segment elevation, and reelevation of CK-MB to more than the upper limit of normal or increased by at least 50% over the previous value. Complications include severe CHF, cardiogenic shock, arrhythmias, cardiac arrest, and death.[86,196] Recurrent MI after fibrinolysis increases the risk of mortality by up to 2 years, but most of the deaths occur in the hospital with little additional risk of death occurring between the time of the index hospitalization and 2 years.[197]

Nitrate and β-blocker therapy should be optimized, and therapeutic anticoagulation should be achieved. Secondary causes of recurrent ischemia (poorly controlled heart failure, anemia, and arrhythmias) should be corrected. Coronary arteriography can clarify the cause of chest discomfort and facilitate PCI or CABG if indicated. Readministration of fibrinolytic therapy may be reasonable for patients who

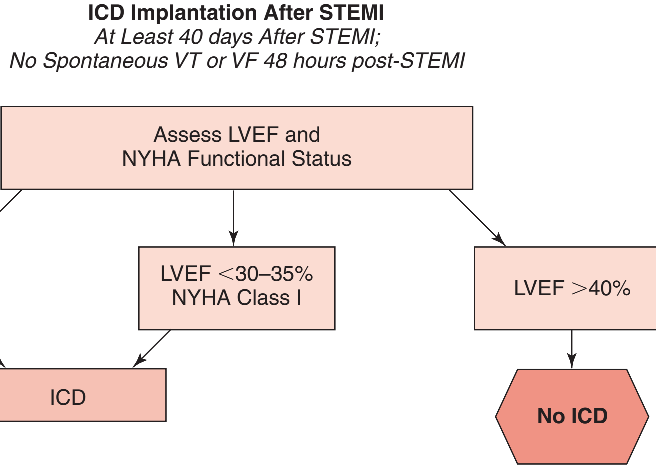


Figure 11–16 Algorithm for assessment of need for implantation of a cardioverter/defibrillator. The appropriate management is selected based upon measurement of left ventricular ejection fraction and assessment of the NYHA functional class. Patients with depressed left ventricular function at least 40 days post-STEMI are referred for insertion of an implantable cardioverter/defibrillator (ICD) if the LVEF is <30–40% and they are in NYHA class II-III or if the LVEF is <30–35% and they are in NYHA class I functional status. Patients with preserved left ventricular function (LVEF >40%) do not receive an ICD regardless of NYHA functional class. All patients are treated with medical therapy post-STEMI. (Adapted from data contained in Zipes DP, Camm AJ, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death; a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines [Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death]. J Am Coll Cardiol 2006;48:1064-1108).

are not considered candidates for revascularization or for whom coronary angiography and PCI cannot be rapidly implemented.

Pericarditis

Pericarditis can complicate transmural STEMI and is associated with larger infarcts, a lower EF, and a higher incidence of CHF.[198,199] Pericarditis may appear up to several weeks after STEMI and can be confused with recurrent ischemia. However, pericardial pain is usually pleuritic and/or positional and radiates to the left shoulder, scapula, or trapezius muscle. Detection of a 3-component rub is diagnostic of pericarditis. The electrocardiogram may demonstrate J-point elevation with concave upward ST-segment elevation and PR depression. A small pericardial effusion on an echocardiogram is not diagnostic of pericarditis. The incidence of pericarditis has decreased in the reperfusion era, and the Dressler syndrome (post-MI syndrome), an autoimmune-type carditis, has essentially disappeared.[200]

Aspirin (160 to 325 mg daily) is the treatment of choice, but high doses (650 mg every 4 to 6 hours) may be required.[201] Colchicine 0.6 mg orally every 12 hours or acetaminophen 500 mg orally every 12 hours can be used if episodes are not controlled with aspirin.[202] Nonsteroidal anti-inflammatory drugs may be considered for pain relief, but they should not be used for extended periods because they can decrease aspirin efficacy and increase the risk of myocardial scar thinning and infarct expansion. Corticosteroids should not be used except as a last resort because they have been associated with scar thinning and myocardial rupture.[203] Antithrombotic therapy can usually be continued safely but requires added vigilance for the detection of enlarging pericardial effusion or signs of hemodynamic instability.

Other Complications

Ischemic Stroke

Acute stroke complicates 0.75% to 1.2% of STEMIs and has a >40% mortality rate.[204] Earlier stroke, hypertension, old age, decreased EF, multiple ulcerated plaques, and AF are the major risk factors for embolic stroke post-STEMI.[205] Embolic stroke post-STEMI originates from LV thrombus or from the left atrium in the setting of atrial fibrillation and occurs even in patients treated with fibrinolysis. Most ischemic cerebral infarctions after fibrinolytic therapy occur more than 48 hours after treatment.[206] The highest risk period is the first 28 days post-STEMI,[207] but risk is elevated for at least up to 1 year. Compared with ICH, patients with ischemic cerebral infarction present more commonly with focal neurologic deficits and less commonly with a depressed level of consciousness. Headache, vomiting, and coma are uncommon.[208]

An algorithm for evaluation and antithrombotic therapy for ischemic stroke is shown in Figure 11–17. Ischemic cerebral dysfunction may be presumed with the sudden onset of a focal neurologic deficit, an initial CT scan negative for blood or mass effect, and the absence of a severe metabolic disorder, seizures, autoimmune disease, or cancer. Neurologic consultation is recommended to assist with planning the neurovascular evaluation and management issues. The location and nature of the ischemic brain lesion should be defined with repeat CT scan or MRI scan. Vascular lesions should be evaluated with noninvasive techniques, such as carotid

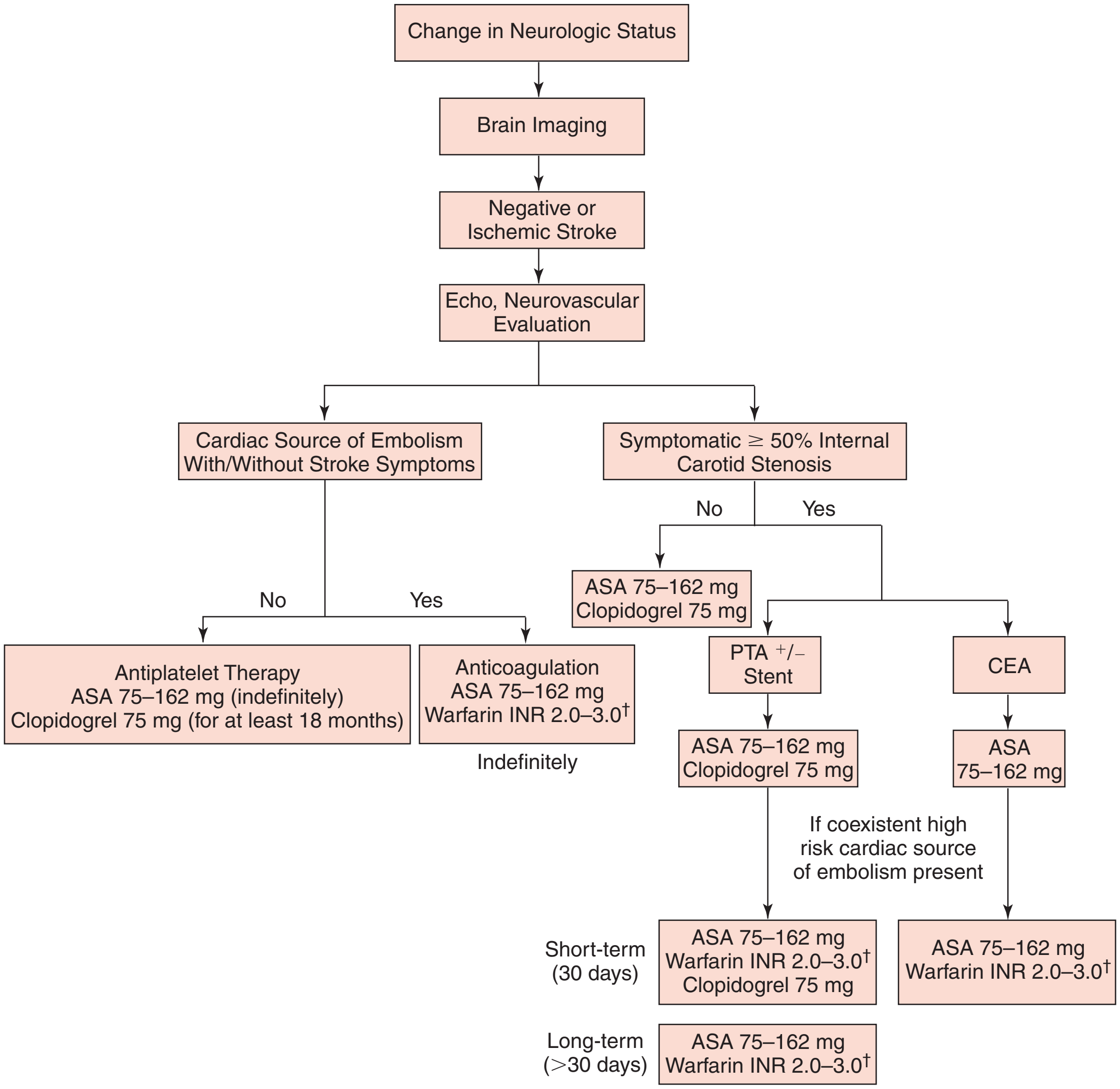


Figure 11–17 Algorithm for post-reperfusion ischemic stroke treatment. Daily doses of antithrombotic therapy are shown in the algorithm. *An INR of 2.0 to 3.0 is acceptable with tight control, but the lower end of the range is preferable. The combination of antiplatelet therapy and warfarin may be considered in patients <75 years of age, with low bleeding risk, and who can be monitored reliably. ASA, aspirin; CEA, carotid endarterectomy; INR, international normalized ratio; PTA, percutaneous transluminal angioplasty (carotid). (Adapted from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. Circulation 2004;110:588-636, with permission.)

duplex sonography, transcranial Doppler, magnetic resonance angiography, CT angiography, or transesophageal echocardiography. For carotid territory symptoms and signs, evidence for a >50% stenosis should be sought.

Both aspirin[34] and clopidogrel[209] reduce the occurrence of ischemic stroke. Patients with cardiogenic sources of embolism, such as AF, LV mural thrombi or akinetic segment of the left ventricular myocardium, should receive moderate intensity (INR 2-3) warfarin anticoagulation in combination with aspirin. In general, STEMI patients with LV mural thrombus should receive 3 months of warfarin therapy. Ischemic stroke patients with preexisting or persistent AF require lifelong warfarin therapy. A significant carotid artery stenosis may require treatment either with carotid stenting or carotid endarterectomy.

Deep Venous Thrombosis and Pulmonary Embolism

Deep venous thrombosis and pulmonary embolism occur infrequently. Low-dose heparin prophylaxis, preferably with a LMWH, should be given to patients with CHF who are unable to ambulate or who are considered at high risk for deep venous thrombosis. Most patients with deep venous thrombosis or pulmonary embolism should be anticoagulated with LMWH.[210] Warfarin should be initiated concurrently with LMWH, and LMWH should be continued until the INR

reaches the therapeutic range of 2 to 3. Warfarin should be continued for a duration specific to the individual patient's risk profile.[211]

Coronary Artery Bypass Surgery

Surgery after STEMI may carry substantial risk, particularly in unstable patients with Q-wave infarction and decreased LV function. Prior coronary artery bypass grafting, female gender, comorbidities, and advanced age are factors that compound this risk considerably.[212] Patients who have mechanical complications of myocardial infarction, such as ventricular septal rupture or papillary muscle rupture, or who have ongoing ischemia that has been unresponsive to other medical therapy and have vessels suitable for bypass, should undergo emergency surgery. Stable patients should have surgery delayed for 3 to 7 days to allow myocardial recovery to occur.

An internal mammary artery graft to a significantly stenosed left anterior descending artery should be used whenever possible owing to better long-term survival (see Chapter 8). Unstable patients undergoing CABG shortly after fibrinolytic therapy, primarily for continuing myocardial ischemia, have a higher operative mortality rate (13% to 17%) and increased use of blood products.[213] CABG should be considered when recurrent ischemia occurs in patients whose coronary artery anatomy is not suitable for PCI. Elective CABG improves survival relative to medical therapy in patients with MI who have (1) left main coronary artery stenosis; (2) left main equivalent disease (significant ≥70% stenosis of the proximal left anterior descending and proximal left circumflex artery); (3) three-vessel disease, particularly with decreased left ventricular function; (4) two-vessel disease with significant proximal left anterior descending stenosis, not amenable to PCI, and either ejection fraction <0.50% or demonstrable ischemia on noninvasive testing; and (5) one- or two-vessel disease, not amenable to PCI, without proximal left anterior descending stenosis but with a large area of viable myocardium at risk and high-risk criteria on noninvasive testing.[214] Aspirin should not be withheld before surgery, but if possible, clopidogrel should be withheld for 5 to 7 days.[40] Platelet aggregation returns to normal 4 hours after discontinuing eptifibatide or tirofiban. Platelet transfusions may need to be given to restore platelet function if surgery is performed within 24 hours of receiving abciximab because of its prolonged effect.

Risk Stratification

The purpose of risk stratification testing is to determine which patients are at increased risk for recurrent ischemic events, congestive heart failure, or sudden death. Major management decisions include whether to refer a patient for cardiac catheterization (Fig. 11–18) or for placement of an ICD (see Fig. 11–16).

Exercise Testing

Exercise testing may be performed to (1) predict the likelihood of a subsequent cardiac event; (2) establish exercise parameters for cardiac rehabilitation; (3) assess functional capacity and the patient's ability to perform tasks at home and at work; (4) evaluate recurrent chest pain; and (5) evaluate the efficacy of the patient's current medical regimen.[215]

Two different protocols have been used. Low-level exercise testing appears to be safe if patients have had no symptoms of angina or heart failure and have a stable baseline ECG 48 to 72 hours before the exercise test. The traditional submaximal exercise test is stopped when one of the following endpoints is reached: peak heart rate of 120 to 130 beats per minute or 70% of maximal predicted for age; peak work level of 5 METs; clinical endpoints of mild angina or dyspnea; ST-segment depression >2 mm; exertional hypotension; or three or more consecutive PVCs. The second protocol is performance of a symptom-limited exercise test in low-risk patients days to weeks after STEMI. Although this will result in a higher frequency of abnormal exercise tests, the prognostic value of ST-segment depression occurring at higher work levels in deconditioned patients is uncertain.

Baseline abnormalities that compromise ECG interpretation include >1 mm ST-segment depression on the resting tracing, LBBB, LV hypertrophy with strain, ventricular pre-excitation, and ventricular pacing. If exercise testing is performed in the presence of these abnormalities, echocardiography or myocardial perfusion imaging should be added. Exercise testing should not be performed within 2 to 3 days of STEMI in patients who have not undergone successful reperfusion. Exercise testing should not be performed to evaluate patients with STEMI who have unstable post-infarction angina, decompensated CHF, life-threatening cardiac arrhythmias, noncardiac conditions that severely limit their ability to exercise, or other absolute contraindications to exercise testing.

Echocardiography

Echocardiography should be used to assess both global and regional ventricular function in patients not undergoing contrast left ventriculography. It should also be used to evaluate suspected complications including RV infarction, acute mitral regurgitation, ventricular septal rupture, cardiogenic shock, infarct expansion, intracardiac thrombus, and pericardial effusion.[216,217]

The incremental value of exercise echocardiography over regular exercising testing after STEMI has not been established. However, echocardiography or perfusion imaging should be added to exercise testing whenever baseline abnormalities are expected to compromise electrocardiographic interpretation. Pharmacologic stress echocardiography using a graded protocol and beginning at low doses of dobutamine can be substituted for exercise in pre-discharge functional testing for ischemia in patients with limited exercise capacity and can help in assessing myocardial viability early after STEMI.

Myocardial Perfusion Imaging

When baseline abnormalities are expected to compromise electrocardiographic exercise test interpretation, myocardial perfusion imaging or echocardiography should be added. An advantage for nuclear scintigraphy is the quantitative measurement of LVEF. Data are also emerging to suggest that dipyridamole or adenosine stress perfusion nuclear scintigraphy is safe and can be used for early (48 to 72 hours) risk stratification.[218]

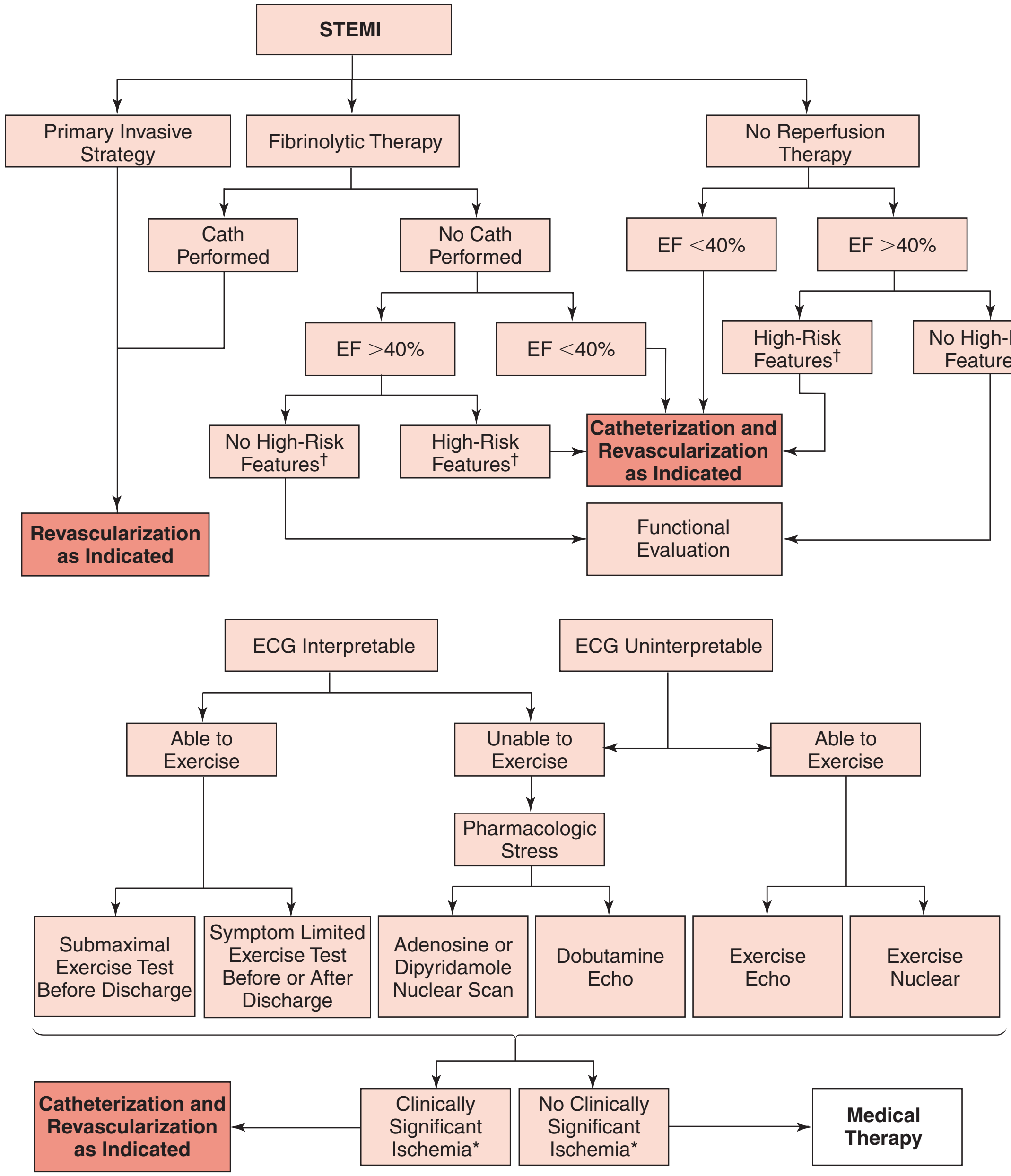


Figure 11–18 Evidence-based approach to need for catheterization (cath) and revascularization after ST-elevation myocardial infarction (STEMI). The algorithm shows treatment paths for patients who initially undergo a primary invasive strategy, receive fibrinolytic therapy, or do not undergo reperfusion therapy for STEMI. Patients who have not undergone a primary invasive strategy and have no high-risk features should undergo functional evaluation with one of the noninvasive tests shown. When clinically significant ischemia is detected, patients should undergo catheterization and revascularization as indicated; if no clinically significant ischemia is detected, medical therapy is prescribed after STEMI. *Please see Table 23 of the ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina for further definition. (Adapted from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. Circulation 2004;588-636, with permission.)

Left Ventricular Function

Assessment of LV function after STEMI has been shown to be one of the most accurate predictors of future cardiac events.[219] The assessment can include such basic factors as clinical estimates based on the patient's symptoms (exertional dyspnea, functional status) and physical findings (rales, murmurs, elevated jugular venous pressure, cardiomegaly, S3 gallop). Measurement of LVEF by contrast ventriculography, radionuclide ventriculography, and two-dimensional echocardiography has important prognostic value. Because of the dynamic nature of LV function recovery after STEMI, the

timing of the imaging study needs to be considered. An LVEF <0.40 is an indication for ACE inhibitor therapy and a reduced EF is useful for identifying candidates for an ICD (see Fig. 11–16). Post-infarction LV dilation, demonstrated by increased end-systolic volume >130 mL, may be a better predictor of mortality after MI than an LVEF <0.40 or increased end-diastolic volume.[220]

Myocardial Viability

In some patients, viable but dysfunctional myocardium contributes to LV dysfunction and may be significantly reversible with revascularization. Processes of myocardial hibernation (chronic low flow states associated with depressed myocardial function)[221] and stunning (depression of ventricular function after acute ischemia despite adequate restoration of blood flow)[222] contribute to the potential reversibility of ventricular function. Radionuclide imaging and dobutamine echocardiography can identify patients most likely to benefit from revascularization.[223] Positron emission tomography[224] and contrast-enhanced magnetic resonance imaging[225] are promising experimental techniques. However, more conclusive diagnostic efficacy studies are needed to demonstrate patient benefit from viability testing before it becomes standard testing.

Invasive Evaluation

All survivors of STEMI who are candidates for revascularization therapy with spontaneous ischemia, intermediate- or high-risk findings on noninvasive testing, hemodynamic or electrical instability, mechanical defects, earlier revascularization, or high-risk clinical features should be considered for coronary arteriography. PCI or CABG may be considered in these patients if they are found to have significant obstructive coronary artery disease. Previous randomized trials testing a strategy of routine catheterization after fibrinolytic therapy suggested that such an approach was deleterious.[226-230] However, those trials were conducted in an era when aspirin was inconsistently administered, high doses of UFH without ACT monitoring were used, and the interventional catheters, radiographic imaging equipment, and supportive antiplatelet agents were suboptimal. Subsequent data suggest that the early invasive strategy is associated with a lower risk of recurrent MI and death (see Fig. 11–7B).[197]

Assessment of Electrical Substrate

A number of noninvasive strategies have been used to identify patients at high risk for arrhythmic events. Signal-averaged electrocardiography identifies delayed, fragmented conduction in the infarct zone in the form of late potentials at the terminus of the QRS complex and represents an anatomic substrate that predisposes the patient to reentrant VT.[231] Heart rate variability, an analysis of the beat-to-beat variation in cycle length, largely reflects the sympathovagal interaction regulating heart rate. Low heart rate variability, indicative of decreased vagal tone, is a predictor of increased mortality, including sudden death, in patients after MI.[232] Baroreceptor sensitivity also quantifies the influence of parasympathetic tone on the heart. It is measured as the slope of a regression line that relates beat-to-beat heart rate change in response to a change in blood pressure, often accomplished by giving a small bolus of phenylephrine.[233] Abnormalities in ventricular repolarization are detectable by microvolt alterations of T wave amplitude, or T wave alternans, and have been shown to be associated with inducible ventricular arrhythmias during programmed ventricular stimulation and spontaneous arrhythmic events.[234] The clinical importance of these tests has yet to be determined.

LONG-TERM MANAGEMENT

Risk Factor Control

Secondary prevention therapies are an essential part of the management of all patients with STEMI. (Table 11–9) Because atherosclerotic vascular disease is frequently found in multiple vascular beds, the physician should also search for symptoms or signs of peripheral vascular disease or cerebrovascular disease in patients with STEMI. Approximately 70% of CHD deaths and 50% of MIs occur in patients who have previously established coronary artery disease.[2] It is estimated that the likelihood of fatal and nonfatal MI is four to six times higher in patients with apparent coronary disease. Within 6 years after a recognized heart attack, 18% of men and 35% of women will have another heart attack[2]; most episodes of cardiac arrest occur within 18 months after hospital discharge for STEMI.[235] Therefore, the institution of secondary prevention therapies and risk reduction strategies in patients recovering from STEMI represent major opportunities to reduce the toll of cardiovascular disease.

Weight Management

Obesity is a recognized major risk factor for cardiovascular disease and an important component of the metabolic syndrome. The diagnosis of metabolic syndrome includes three of the following: waist circumference >40 inches in men and >35 inches in women; TG ≥250/dL; HDL <40 mg/dL in men or <50 mg/dL in women; blood pressure >130/85 mm Hg; and fasting blood glucose ≥110 mg/dL. The primary treatment strategies are calorie control and physical activity. A desirable BMI range is 18.5 to 24.9 kg/m^2. Weight loss should be part of the cardiac rehabilitation program after STEMI with a goal of losing 10% of body weight over 6 months at a rate of 1 to 2 pounds each week.

Smoking Cessation

Smoking increases coronary vasomotor tone, reduces the anti-ischemic effects of β-adrenoceptor blockers, and doubles mortality after STEMI.[236] Smoking cessation reduces rates of reinfarction and death within a year of quitting, but one third to one half of patients relapse within 6 to 12 months.[237] Family members who live in the same household should also be encouraged to quit smoking to help reinforce the patient's effort and to decrease the risk of second-hand smoke. The most effective pharmacologic adjuncts for treating nicotine dependence are nicotine replacement therapy (gums and patches) and bupropion, combined with behavioral counseling.[238]

Table 11–9 Secondary Prevention for Patients with STEMI

Goals	Intervention Recommendations
Smoking *Goal:* Complete cessation	Assess tobacco use. Strongly encourage patient and family to stop smoking and to avoid second-hand smoke. Provide counseling, pharmacologic therapy (including nicotine replacement and bupropion) and formal smoking cessation programs as appropriate.
Blood pressure control: *Goal:* <140/90 mm Hg or <130/80 mm Hg if chronic kidney disease or diabetes	If blood pressure is 120/80 mm Hg or greater: • Initiate lifestyle modification (weight control, physical activity, alcohol moderation, moderate sodium restriction, and emphasis on fruits, vegetables, and low-fat dairy products) in all patients. If blood pressure is 140/90 mm Hg or greater or 130/80 mm Hg or greater for individuals with chronic kidney disease or diabetes • Add blood pressure-reducing medications, emphasizing the use of β-blockers and inhibitors of the renin-angiotensin-aldosterone system.
Lipid management: (TG < 200 mg/dL) *Primary goal:* LDL-C substantially <100 mg/dL and preferably ≤70 mg/dL	Start dietary therapy in all patients (<7% of total calories as saturated fat and <200 mg/day cholesterol). Promote physical activity and weight management. Encourage increased consumption of omega-3 fatty acids. Assess fasting lipid profile in all patients, preferably within 24 hours of STEMI. Add drug therapy according to the following guide: LDL-C <100 mg/dL (baseline or on-treatment): • Statins should be used to lower LDL-C LDL-C ≥100 mg/dL (baseline or on-treatment): • Intensify LDL-C-lowering therapy with drug treatment, giving preference to statins.
Lipid management: (TG 200 mg/dL or greater) *Primary goal:* Non-HDL-C* <130 mg/dL	If TGs are ≥150 mg/dL or HDL-C is <40 mg/dL: • Emphasize weight management and physical activity. Advise smoking cessation. If TG is 200–499 mg/dL: • After LDL-lowering therapy,† consider adding fibrate or niacin‡ If TG is ≥ 500 mg/dL: • Consider fibrate or niacin‡ before LDL-C-lowering therapy† • Consider omega-3 fatty acids as adjunct for high TG
Physical activity: *Minimum goal:* 30 minutes 3 to 4 days per week Optimal daily	Assess risk, preferably with exercise test, to guide prescription. Encourage minimum of 30 to 60 minutes of activity, preferably daily, or at least 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (walking breaks at work, gardening, household work). Cardiac rehabilitation programs are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted.
Weight management: *Goal:* BMI 18.5-24.9 kg/m^2 Waist circumference: Women: <35 inches Men: <40 inches	Calculate BMI and measure waist circumference as part of evaluation. Monitor response of BMI and waist circumference to therapy. Start weight management and physical activity as appropriate. Desirable BMI range is 18.5–24.9 kg/m^2. If waist circumference is ≥35 inches in women or ≥40 inches in men, initiate lifestyle changes and treatment strategies for metabolic syndrome.
Diabetes management: *Goal:* $HbA1_c$<7%	Appropriate hypoglycemic therapy to achieve near-normal fasting plasma glucose, as indicated by HbA1c. Treatment of other risk factors (physical activity, weight management, blood pressure, and cholesterol management).
Antiplatelet Agents/Anticoagulants	Start and continue indefinitely aspirin 75 to 162 mg/day if not contraindicated. Start clopidogrel 75 mg/day. Manage warfarin to INR 2.5 to 3.5 in post-STEMI patients when clinically indicated or for those not able to take aspirin or clopidogrel.

Lipid Management

Dietary therapy that is low in saturated fat and cholesterol (<7% of total calories as saturated fat and <200 mg/day cholesterol) should be started after recovery from STEMI. Patients should increase consumption of omega-3 fatty acids, fruits, vegetables, soluble (viscous) fiber, and whole grains. The Heart Protection Study[239] and the PROVE-IT-TIMI 22 trial,[240] among others,[241] suggest that the goal for statin therapy in these patients should be to lower the LDL cho-

Table 11–9 Secondary Prevention for Patients with STEMI—cont'd

Goals	Intervention Recommendations
Renin-Angiotensin-Aldosterone System Blockers:	ACE inhibitors in all patients indefinitely; start early in stable high-risk patients (anterior MI, previous MI, Killip ≥II [S3 gallop, rales, radiographic CHF], LVEF <0.40). Angiotensin-receptor blockers in patients who are intolerant of ACE inhibitors and with either clinical or radiologic signs of CHF or LVEF <0.40. Aldosterone blockade in patients without significant renal dysfunction§ or hyperkalemia‖ who are already receiving therapeutic doses of an ACE inhibitor, have an ≤0.40, and have either diabetes or heart failure.
β-Blockers:	Start in all patients. Continue indefinitely. Observe usual contraindications.

*Non-HDL-C, total cholesterol minus HDL-C.
†Treat to a goal of non-HDL-C substantially <130 mg/dL
‡Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician.
§Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women.
‖Potassium should be <5.0 mEq/L.
ACE, angiotensin-converting enzyme; BMI, body mass index; CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; STEMI, ST-elevation myocardial infarction; TG, triglycerides.
Modified from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.

lesterol to 70 mg/dL. Approximately 25% of patients who have recovered from STEMI demonstrate desirable total cholesterol values but a low HDL level. Low HDL is an independent risk factor for the development for CAD.[242] Patients with non-HDL cholesterol levels <130 mg/dL who have HDL levels <40 mg/dL should receive special emphasis on nonpharmacologic therapy (i.e., exercise, weight loss) to increase HDL. Those who do not respond may be started on fibrates or niacin. It is reasonable to add either niacin or fibrates to the diet regardless of LDL and HDL levels when triglyceride levels are >500 mg/dL. In this setting, non-HDL cholesterol (goal <130 mg/dL) should be the cholesterol target, rather than LDL. Diet and drug treatment are also effective in the elderly.[243] Patients started on lipid-lowering therapy before hospital discharge are three times more likely to be taking medication at 6 months than those who start therapy after discharge.[244]

Blood Pressure Control

Lifestyle modifications for patients with blood pressure >120/80 mm Hg include weight reduction if overweight or obese; consumption of a diet rich in fruits and vegetables and low in total fat and saturated fat; and reduction of sodium to no more than 2.4 g/day. A diet rich in potassium and calcium is also recommended for those with normal renal function. After STEMI, patients should be treated with β-blockers, ACE inhibitors (or ARBs if ACE inhibitors are not tolerated), and, if necessary, aldosterone antagonists to a target BP of <140/90 mm Hg. Patients with chronic kidney disease or diabetes should be treated to a target <130/80 mm Hg.[245] Most patients will require two or more drugs to reach goal, and when the BP is >20/10 mm Hg above goal, two drugs should usually be used from the outset. Thiazides or long-acting calcium channel blockers may be used if other agents are not tolerated or are not sufficient to reach BP goal. Short-acting calcium antagonists should not be used.

Diabetes Management

Tight glucose control (HbA1c <7.0%) in diabetics during and after STEMI has been shown to lower acute and 1-year mortality rates.[246] Thiazolidinediones are frequently used as monotherapy or in combination with other oral hypoglycemic agents, insulin, and diet for control of diabetes. Thiazolidinediones may also be associated with fluid retention and an increase in left ventricular preload[247] that is resistant to diuretics, so they should not be used in patients recovering from STEMI who have NYHA class III or IV heart failure.[248] Patients with heart failure and/or significant renal insufficiency should not be placed on metformin.

Medications

Antiplatelet Agents

The Antiplatelet Trialists' Collaboration reported a 25% reduction in the risk of recurrent infarction, stroke, or vascular death in patients who received prolonged antiplatelet therapy (36 fewer events for every 1000 patients treated).[36] No antiplatelet therapy has proved superior to aspirin, and daily doses of aspirin between 75 and 160 mg should be continued indefinitely. The salutary effect of aspirin may be diminished by the concomitant use of ibuprofen and other NSAIDs[249,250] and this combination should be discouraged. Clopidogrel is the best alternative to aspirin in patients who have a true aspirin allergy.[251] Dual antiplatelet therapy with aspirin and clopidogrel should be continued for several weeks in patients who are not treated with PCI and for several months in patients who receive PCI.[38,39]

β-Blockers

The benefits of β-blocker therapy in patients without contraindications are well established with or without reperfusion therapy and in all age groups. The greatest mortality benefit is seen in patients with impaired left ventricular function, ventricular arrhythmias, and occluded infarct arteries. The benefit is less in low-risk patients, but β-blockers may still minimize the likelihood of recurrent ischemic symptoms and control heart rate and blood pressure during exertion. In patients with moderate or severe LV failure, β-blocker therapy should be administered using a gradual titration scheme.[252] Even when relative contraindications exist (mild asthma not currently active, insulin-dependent diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, PR interval >0.24 seconds, moderate LV failure), the benefit in reducing mortality and reinfarction with β-blocker therapy may outweigh the risks. Data from large trials suggest that therapy should be continued for at least 2 to 3 years and probably should be continued indefinitely.

Statins

Statin therapy reduces the risk of myocardial infarction, stroke, and death in all subgroups.[240,253-255] Benefit has been shown at all levels of LDL, although the greatest benefit was seen with LDL >125 mg/dL. A strong argument can be made for starting all patients on statin therapy, regardless of their LDL level. The treatment goal should be a LDL level substantially <100 mg/dL and probably closer to 70 mg/dL.[240]

Inhibition of the Renin-Angiotensin-Aldosterone System

ACE inhibitors inhibit ventricular remodeling and dilatation after STEMI and should be prescribed at discharge for all patients without contraindications to decrease the risk of MI, CHF, and death.[256-259] Although the largest benefit appears to be in those with ejection fractions below 40% and with anterior MI, other trials have shown benefit in patients without known left ventricular dysfunction or CHF.[260,261]

Angiotensin receptor blockers should be prescribed for those STEMI patients who are intolerant of ACE inhibitors and have either clinical or radiologic signs of heart failure and a LVEF >40%. Valsartan[262] may be initiated at 20 mg/day and titrated to a maximum of 160 mg twice a day. Candesartan[263] can be initiated at 4 to 8 mg daily and titrated to 32 mg daily.

An aldosterone inhibitor (spironolactone—target dose 50 mg or eplerenone—target dose 50 mg) should be added to an ACE inhibitor or ARB in patients with LVEF <40% and CHF or diabetes, provided the serum creatinine is <2.5 mg/dL in men, or 2.0 mg/dL in women, and the serum potassium is <5.0 mEq/L.[124,125]

Warfarin

The indications for long-term anticoagulation after STEMI are controversial and evolving. Markers of thrombin generation remain elevated after STEMI and recurrent ischemic events occur even in the presence of aspirin and clopidogrel. In the APRICOT study,[264] the use of medium intensity warfarin (INR 2 to 3) plus aspirin resulted in less infarct artery reocclusion after fibrinolytic therapy and a significant reduction in the combined endpoints of death, MI, and revascularization versus aspirin alone. The WARIS II trial[265] compared high-intensity warfarin (INR 2.8 to 4.2) alone, medium-intensity warfarin (INR 2 to 2.5) plus aspirin 81 mg, and aspirin 160 mg alone. There was a significant reduction in nonfatal MI and nonfatal thromboembolic stroke with warfarin, but bleeding was more common and a significant number of patients discontinued therapy. Patients >75 years of age have not been adequately studied.

When the physician thinks that there is a significant risk for reinfarction or thromboembolic events and a low risk for bleeding in patients <75 years of age, it is reasonable to prescribe warfarin alone (INR 2.5 to 3.5) or warfarin (INR 2 to 3) in combination with aspirin 81 to 162 mg to those who can have their level of anticoagulation monitored reliably (Fig. 11–19). Warfarin may be used in aspirin-allergic patients who have indications for anticoagulation. Warfarin should be used in STEMI patients with persistent or paroxysmal AF. It should be prescribed for LV thrombus noted on an imaging study for at least 3 months and may be useful when extensive regional wall motion abnormalities are present. When the combination of warfarin, aspirin, and clopidogrel is required, clopidogrel should be stopped as soon as possible.[266,267]

Hormone Replacement Therapy

Postmenopausal women should not receive combination estrogen and progestin therapy for secondary prevention.[268,269] It is recommended to discontinue use of hormone therapy for women who have STEMI.[270] Women who are beyond 1 to 2 years post-initiation of hormone therapy and wish to continue it should weigh the risks and benefits, recognizing a greater risk of cardiovascular events. Hormone therapy should not be continued while patients are at bed rest in the hospital because of the increased risk for venous thromboembolic events.

Antioxidants

Vitamin E supplementation does not reduce cardiac events after STEMI,[271] nor are there data supporting vitamin C supplementation. Beta carotene has no beneficial effect and may increase the risk of lung cancer.[272] The use of either lipid- or water-soluble antioxidant supplementation should be discouraged.

Functional Status

Physical Activity

Walking can be encouraged immediately after discharge. In stable uncomplicated patients, sexual activity with the usual partner can be resumed within 1 week to 10 days. Driving can begin a week after discharge if the patient is judged to be in compliance with individual state laws. Air travel within the first 2 weeks of STEMI should be undertaken only in the absence of angina or dyspnea at rest. Based on assessment of risk, ideally with an exercise test to guide the prescription, all patients recovering from STEMI should be encouraged to exercise for a minimum of 30 minutes, preferably daily, but at

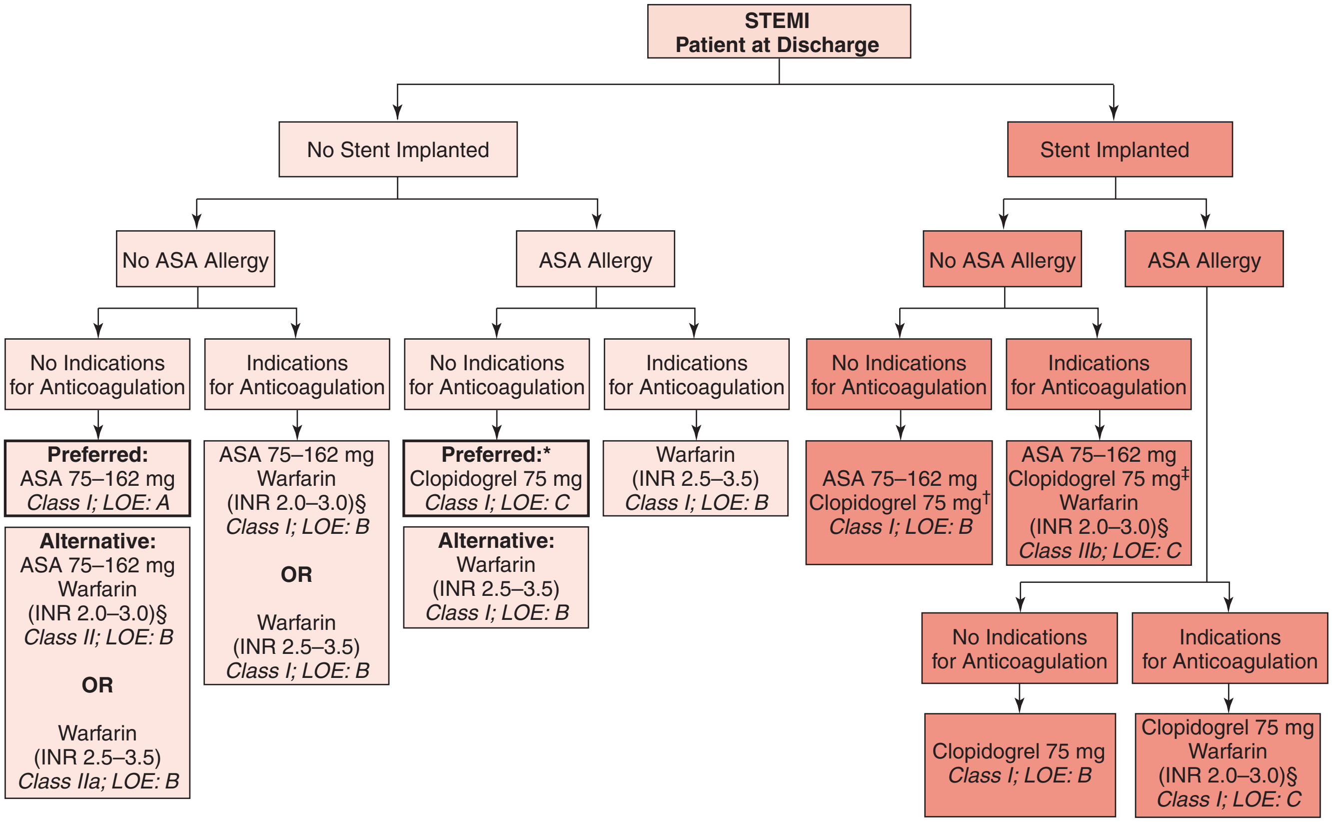


Figure 11–19 Long-term antithrombotic therapy at hospital discharge after ST-elevation myocardial infarction (STEMI). *Clopidogrel is preferred over warfarin because of increased risk of bleeding and low patient compliance in warfarin trials. †For 12 months. ‡Discontinue clopidogrel 1 month after implantation of a bare-metal stent or several months after implantation of a drug-eluting stent (3 months after sirolimus and 6 months after paclitaxel) because of the potential increased risk of bleeding with warfarin and two antiplatelet agents. Continue aspirin and warfarin long term if warfarin is indicated for other associated reasons such as atrial fibrillation, LV thrombus, cerebral emboli, or extensive regional wall-motion abnormality. §An INR of 2.0 to 3.0 is acceptable with tight control, but the lower end of this range is preferable. The combination of antiplatelet therapy and warfarin may be considered in patients <75 years of age with low bleeding risk who can be monitored reliably. ASA, aspirin; INR, international normalized ratio; LOE , level of evidence. (Adapted from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. Circulation 2004;110:588-636, with permission.)

least 3 or 4 times per week (walking, jogging, cycling, or other aerobic activity). The 30 minutes can be spread out over two or three segments during the day. This should be supplemented by an increase in daily lifestyle activities (such as walking breaks at work, gardening, household work). Patients also require specific instruction on strenuous activities (such as heavy lifting, climbing stairs, yard work, household activities) that are permissible and those they should avoid. In addition to aerobic training, mild-to-moderate resistance training is also recommended. This can be started 2 to 4 weeks after aerobic training has begun.[273]

Cardiac Rehabilitation

Comprehensive cardiac rehabilitation services include long-term programs that involve medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling.[274] These programs are designed to limit the physiologic and psychological effects of cardiac illness, reduce the risk for sudden death or reinfarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of select patients. Enrollment in a cardiac rehabilitation program after discharge may enhance patient education and compliance with the medical regimen as well as assist with the implementation of a regular exercise program. A cardiac rehabilitation program is recommended for all patients, particularly for those with multiple modifiable risk factors and/or for those moderate- to high-risk patients in whom supervised exercise training is warranted.

Psychosocial Impact

Major depression may occur in 15% to 20% of patients and minor depression in as many as 50%.[275] These patients are more likely to be rehospitalized within 1 year and have a decreased long-term survival. They are also less likely to complete cardiac rehabilitation, comply with lifestyle changes and

medication prescriptions, return to work, or resume a normal quality of life. Therefore, the psychosocial status of the patient should be evaluated, including inquiries regarding symptoms of depression, anxiety, or sleep disorders, and the social support environment. Treatment of depression with combined cognitive-behavioral therapy and selective serotonin reuptake inhibitors improves outcome in terms of depressive symptoms and social function.[276]

Follow-Up Visit

A caring and supportive doctor–patient relationship is vital to the well-being of the survivors and their families. It is common practice to see these patients 3 to 6 weeks after hospital discharge to assess their progress. The following issues should be addressed: (1) the presence or absence of cardiovascular symptoms and the functional state of the patient should be delineated; (2) the list of current medications should be verified and reevaluated—doses of β-blockers, ACE inhibitors, and statins should be titrated when appropriate; (3) the risk assessment work-up should be completed and reviewed—this should include a check of LV function and possibly Holter monitoring for those patients whose early post-STEMI ejection fraction was 30% to 40% or lower, in consideration of possible ICD use; (4) the physician should review the principles of secondary prevention with the patient and the family; (5) the psychosocial status of the patient should be evaluated including inquiries regarding symptoms of depression, anxiety, sleep disorders, and the social support environment—appropriate therapy with cognitive-behavioral therapy and antidepressants should be initiated if indicated; (6) discussion of the resumption of physical activity, return to work, resumption of sexual activity, and travel should occur; (7) patients and their families should be asked if they are interested in CPR and AED training; (8) the physician should review with the patient the risk of reinfarction, symptoms of angina and STEMI, and the advisability of calling 911 if symptoms are unimproved or worsening 5 minutes after a sublingual nitroglycerin tablet; and (9) cardiac rehabilitation programs, where available and appropriate, should be recommended.

Return to Work and Disability

Return to work rates and disability rates are influenced by multiple factors. Besides the cardiac functional status of the patient, factors such as age, depressive symptoms, job security, job satisfaction, financial stability, and company policies all influence the ability and decision to return to work.

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Chronic Stable Angina

David E. Newby and Keith A. A. Fox

CHAPTER CONTENTS

Stable or predictable angina on effort occurs not only in the setting of a fixed atherosclerotic stenosis but also in other conditions such as aortic stenosis, mitral valve prolapse, and hypertrophic cardiomyopathy. In this chapter, we discuss chronic stable angina principally in relation to obstructive coronary atheroma. It should, however, be recognized that other forms of angina exist (Table 12–1) and that vasospasm associated with nonobstructive atheromatous plaques can occur.

EPIDEMIOLOGY

Coronary atherosclerosis is associated with many risk factors, such as cigarette smoking, hyperlipidemia, family history, hypertension, and diabetes mellitus (see Chapter 9).[1] The prevalence and extent of coronary atheroma and angina pectoris increase with age and have a male preponderance.[2] Distribution among ethnic groups is unequal, with higher rates in Indo-Asians and lower rates in East Asians and Afro-Caribbeans compared with whites.[3]

The epidemiology of coronary artery disease and angina pectoris is changing. In some regions of the world, such as North America, Western Europe, Japan, and Australia, the incidence, mortality rates, and in-hospital case fatalities are declining,[4] although the overall prevalence of coronary artery disease is still rising—in keeping with an aging population. However, Eastern Europe, in particular, is experiencing escalating rates of coronary artery disease and associated mortality rates.

NATURAL HISTORY

Angina pectoris results in substantial morbidity. In two thirds of patients, angina has significant effects on the ability to work and to undertake recreational, sexual, and other daily activities. On average, a patient with angina pectoris will consult a primary health care professional two or three times each year. The complications of angina pectoris in part relate to the extent and severity of coronary artery disease and include MI, congestive heart failure, dysrhythmias, and sudden cardiac death. In general, patients with stable angina pectoris have a 2.5% to 5% risk of death or nonfatal myocardial infarction (MI) each year.[5,6]

The likelihood of sustaining an acute MI increases with the severity and extent of atheromatous involvement of the coronary arteries (Fig. 12–1). In addition, left ventricular function and the frequency and severity of angina (Figs. 12–2 and 12–3), as well as demographics such as age and gender, all influence the risk of MI.[7,8]

ASSESSMENT AND INVESTIGATION

Clinical Assessment

In patients with chronic stable angina, episodes of angina are usually initiated at consistent levels of physical stress and promptly disappear with cessation of activity (Table 12–2). Worsening angina provoked by progressively less exertion, over a short period of time, often culminating in pain at rest, is indicative of unstable angina (see Chapter 10).

The likelihood of coronary artery disease as the etiologic factor in the presence of chest pain is increased by the presence of established risk factors. Beyond stigmata of hyperlipidemia (rare) or signs of peripheral atheromatous vascular disease, there usually are no physical signs of angina. However, patients should be examined for signs of other possible causes of anginal chest pain, such as aortic stenosis and hypertrophic obstructive cardiomyopathy.

Risk Stratification

Clinical Indicators

There are a number of clinical indicators that identify patients who are at a relatively high risk for clinical events (Table 12–3 and Fig. 12–4). The threshold for the consideration of coronary angiography should, therefore, be lower in high-risk patients than in those being considered purely on the basis of their symptoms. The list of high-risk indicators in Table 12–3 is not comprehensive but incorporates the principal factors that determine risk.

Noninvasive Evaluation

Resting Electrocardiogram

A resting electrocardiogram (ECG) should always be recorded as part of the diagnostic evaluation of patients with chronic stable angina. (The resting ECG may also be useful for

Table 12–1 Causes of Anginal Chest Pain Not Attributable to a Fixed Atheromatous Stenosis of the Coronary Artery

Vascular Disorders	Cardiac Disorders
Variant angina Atheroma-associated vasospasm Microvascular angina, or syndrome X	Hypertrophic cardiomyopathy Aortic stenosis Hypertensive heart disease and left ventricular hypertrophy Mitral valve prolapse Severe pulmonary hypertension and right ventricular hypertrophy

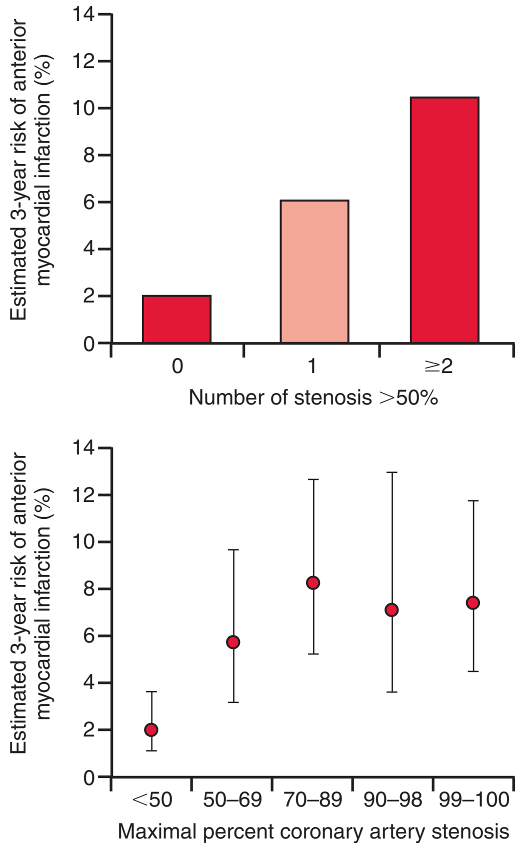


Figure 12–1 Three-year risk of anterior myocardial infarction according to the number *(top)* and severity (*bottom;* mean ± 95% confidence interval) of coronary artery stenoses in the left anterior descending coronary artery. (Data from Ellis S, Alderman E, Cain K, et al: Prediction of risk of anterior myocardial infarction by lesion severity and measurement method of stenoses in the left anterior descending coronary distribution: A CASS Registry study. J Am Coll Cardiol 1988;11:908.)

adjusting medical therapy, e.g., titration of dose of β-blocker). Although the sensitivity of the ECG is low for the diagnosis of ischemic heart disease—normal in almost one half of patients presenting with ischemic heart disease[9]—it does provide prognostic information. Resting ST-segment depression predicts an increased likelihood of subsequent MI and death.[10] Patients with evidence of previous MI or ST-T wave abnormalities without transmural Q-wave MI have a reduced survival rate.[11,12]

Table 12–2 Canadian Cardiovascular Society Functional Classification of Stable Angina Pectoris

Class 1	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class 2	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class 3	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight in normal conditions.
Class 4	Inability to carry on any physical activity without discomfort (anginal syndrome may be present at rest).

From Cox J, Naylor CD: The Canadian Cardiovascular Society grading scale for angina pectoris: Is it time for refinements? Ann Intern Med 1992;117:677.

Table 12–3 Clinical Indicators of Adverse Prognosis in Patients with Chronic Stable Angina

- Previous myocardial infarction
- Recent episode of unstable angina or new-onset stable angina
- Coexisting heart failure or evidence of left ventricular dysfunction
- Coexisting risk factors for coronary artery disease, such as hypertension and diabetes mellitus
- Age—the likelihood of death or nonfatal ischemic event increases with age
- Family history—independent predictor of death
- Pattern of anginal symptoms—quiescent angina is associated with a reduced risk of death and cardiac ischemic events

Exercise Electrocardiogram

Exercise testing is usually performed for two principal reasons: the diagnosis of ischemic heart disease and an assessment of the prognosis. It is an inappropriate screening test for ischemic heart disease when used in isolation. In a population

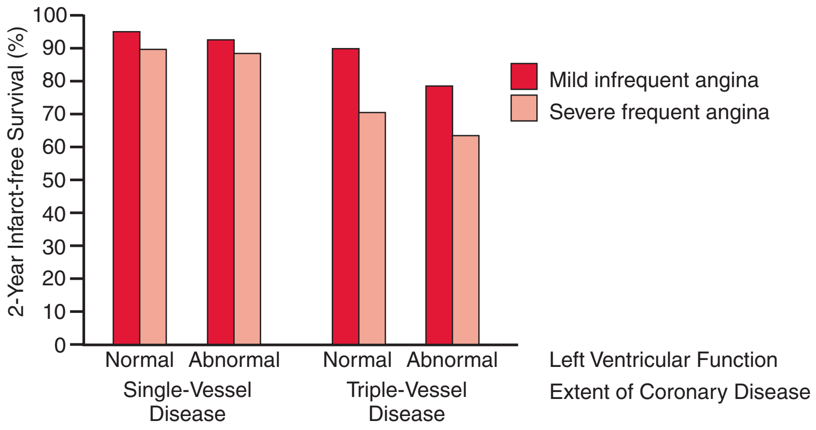


Figure 12–2 Two-year infarction-free survival rate of patients with angina pectoris according to angina frequency, extent of coronary artery disease, and left ventricular function (ejection fraction: normal, ≥50%; abnormal, <50%). (Data from Califf RM, Mark DB, Harrell FE, et al: Importance of clinical measures of ischemia in the prognosis of patients with documented coronary artery disease. J Am Coll Cardiol 1988;11:20.)

with a low prevalence of ischemic heart disease, the false-positive rate is high, particularly in the absence of symptoms (Fig. 12–5). The false-positive rate is also higher in younger individuals and in women.

The clinical context, associated symptoms, and overall cardiovascular response to exercise can be as important as the electrocardiographic response to exercise itself (Table 12–4). When used appropriately, exercise testing is a reliable, easily performed, and robust method of risk stratification in patients with stable angina.[7,13-15] It is a particularly useful method of identifying those individuals at highest risk and those who would benefit from further and potentially more invasive investigation and intervention (Fig. 12–6; see Fig. 12–4).

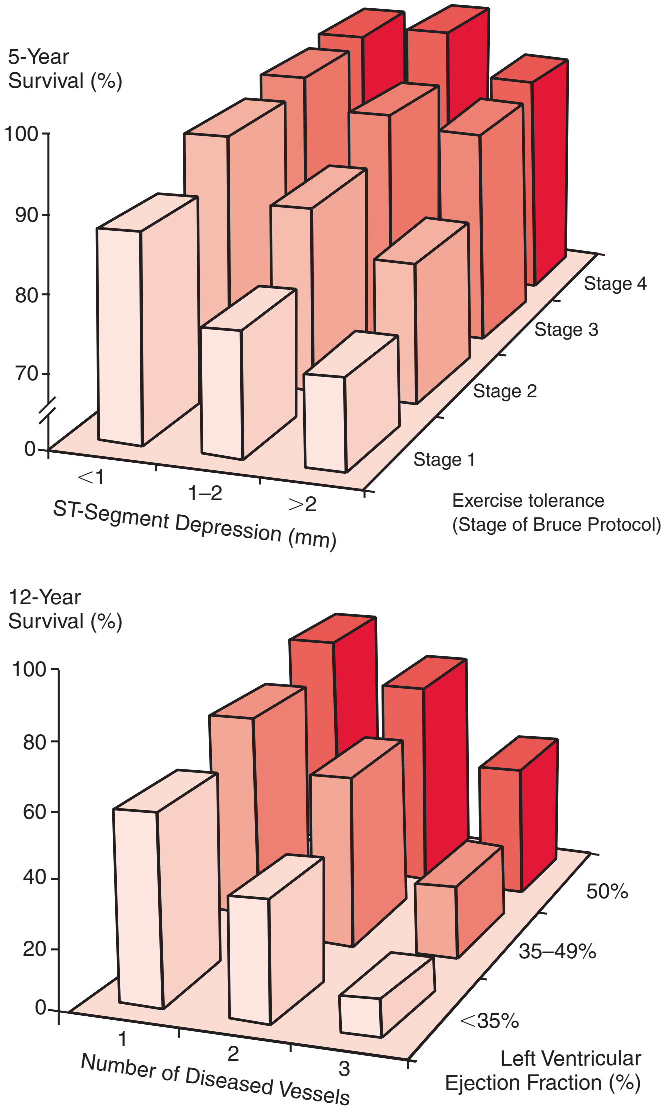


Figure 12–3 Five- and 12-year survival rates of medically treated patients according to exercise tolerance, exercise-induced ST-segment depression, number of diseased vessels, and left ventricular function. (Data from Emond M, Mock MB, David KB, et al: Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation 1994;90:2645; and Weiner DA, Ryan TJ, McCabe CH, et al: Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. J Am Coll Cardiol 1984;3:772.)

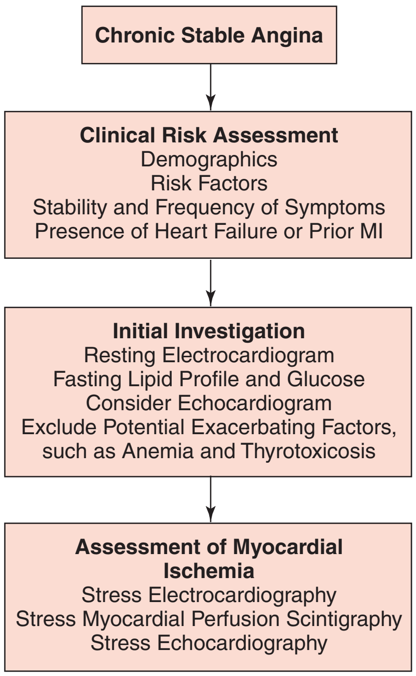


Figure 12–4 Schema for the initial assessment and investigation of patients with chronic stable angina. *Note:* When assessing the patient for provocable ischemia, clinicians should select one of the methods shown but not perform all three.

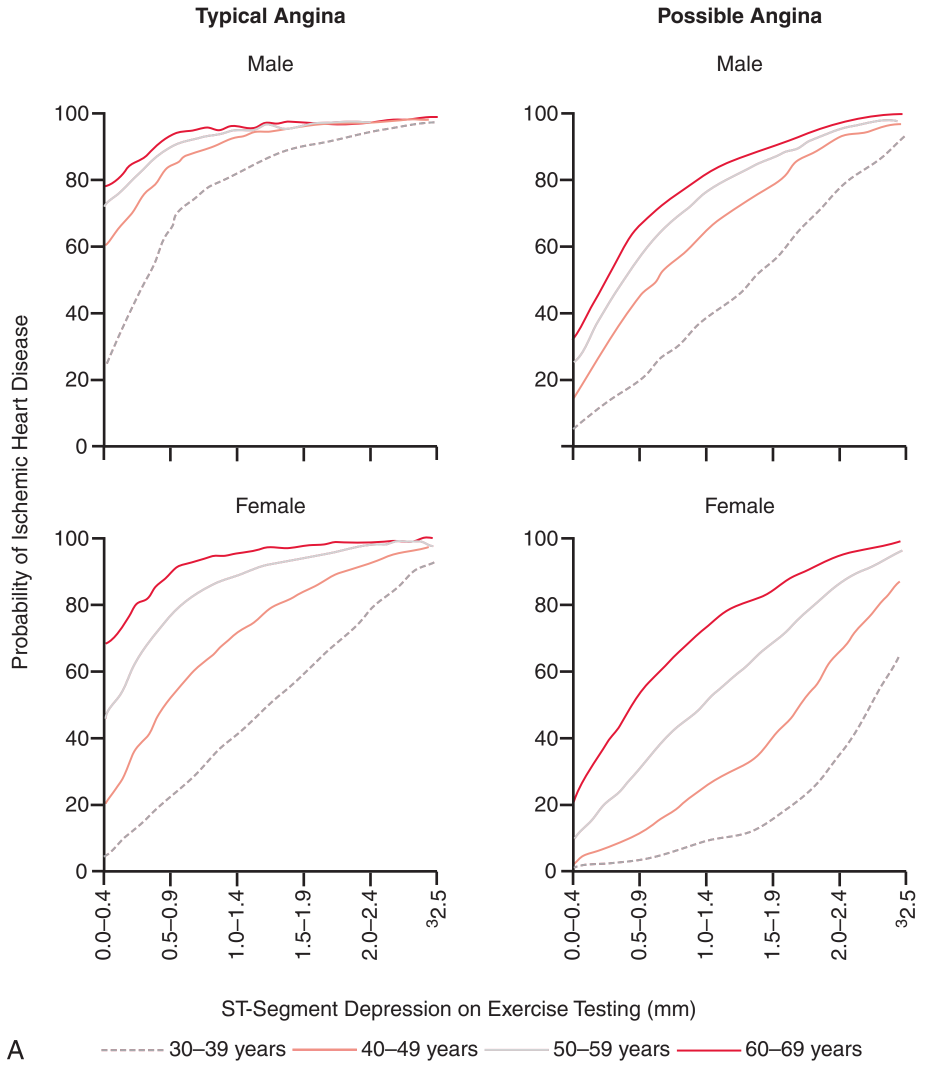


Figure 12–5 Probability of ischemic heart disease according to age, sex, clinical history, and exercise electrocardiographic ST-segment depression. Panel **A** depicts the probability of ischemic heart disease in patients presenting with either typical or possible angina (stratified by gender and age). Panel **B** is arranged similarly but for patients who present with atypical angina or who are asymptomatic. (Data from European Society of Cardiology Working Group on Exercise Physiology, Physiopathology and Electrocardiography: Guidelines for cardiac exercise testing. Eur Heart J 1993;14:969.)

Continued

Stress Myocardial Perfusion Scintigraphy

Stress myocardial perfusion imaging or scintigraphy is a more accurate method of diagnosing ischemic heart disease than exercise testing,[16] with a sensitivity of 80% versus 68% and a specificity of 92% versus 84%, respectively. However, stress myocardial scintigraphy adds little additional information for patients already identified as high risk through the use of conventional exercise testing. It is particularly helpful in those individuals who have equivocal exercise electrocardiographic changes, an abnormal resting ECG, suspected false-positive or false-negative exercise ECG, or submaximal exercise tolerance.

Table 12–4 Features on Exercise Electrocardiogram that are Particularly Associated with a Poor Prognosis and Indicative of Severe Disease

- Poor maximal exercise capacity (<3 of the Bruce protocol)
- ≥1-mm ST-segment depression during stage 2 or less (Bruce protocol)
- ≥2-mm ST-segment depression at any time
- Limited blood pressure response (fall or no rise from baseline)

It may also prove useful in identifying the territory of ischemia in patients with multivessel disease where selective revascularization strategies, such as culprit lesion angioplasty, are being considered. The identification of "hibernating" myocardium may be of particular benefit in patients with left ventricular dysfunction who have the most to gain from coronary revascularization.

Normal stress myocardial scintigraphy is associated with an excellent prognosis (less than 1% annual risk of a major adverse cardiac event even in patients who are known to have ischemic heart disease).[17,18] However, severe and extensive perfusion defects identify patients at a high risk of future cardiac events and a poor prognosis (Table 12–5).[19]

Table 12–5 Features on Stress Myocardial Perfusion Scintigraphy that are Particularly Associated with a Poor Prognosis and Indicative of Severe Disease

- Reversible radionuclide perfusion defect in more than one territory
- Reduced radionuclide ejection fraction with exercise
- Increased lung uptake of radionuclide

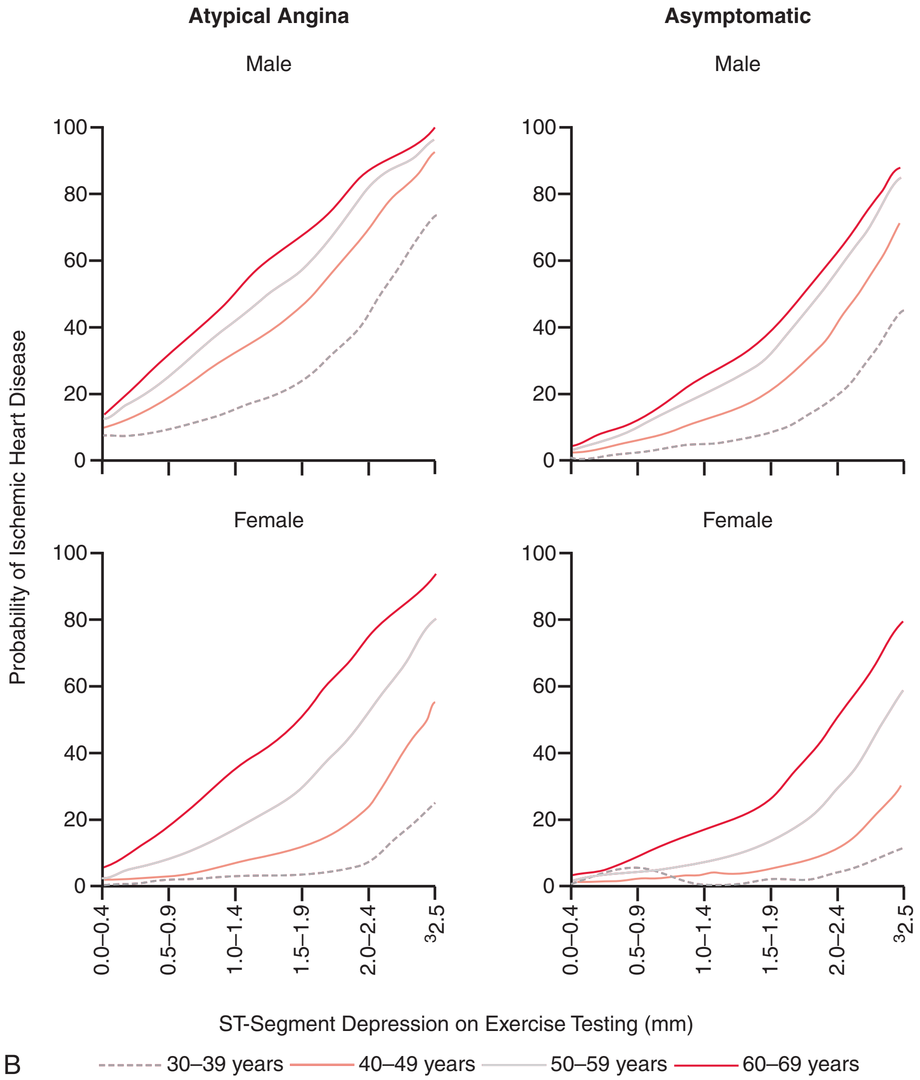


Figure 12–5, cont'd

Resting and Stress Echocardiography

Left ventricular dysfunction at rest or with exercise identifies patients with a poor prognosis.[7,20] As with myocardial scintigraphy, stress echocardiography is a sensitive and specific method of identifying patients with ischemic heart disease[21,22] and facilitates the identification of patients with left ventricular dysfunction and hibernating myocardium who would potentially benefit from coronary revascularization.

Selection and Frequency of Noninvasive Stress Testing

There are significant advantages and disadvantages with each of the three main noninvasive modalities of stress testing (Fig. 12–7 and Table 12–6). Exercise electrocardiographic testing is easily performed, has been extensively validated, and remains the noninvasive test of choice for the majority of patients. However, the sensitivity and specificity of exercise electrocardiography are reduced by intraventricular conduction defects, repolarization abnormalities, poor exercise tolerance, and concomitant cardiac medications such as digitalis.

There are no clear guidelines as to how frequently stress testing should be undertaken in patients with chronic stable angina.[23] After the initial prognostic assessment, recurrent stress testing is unlikely to be helpful unless there are new or changing symptoms or the patient has undergone, or is being considered for, an intervention such as coronary revascularization.[23]

Computed Tomography

Coronary artery calcification is an independent risk factor for coronary heart disease, with even low coronary calcium scores doubling the risk of coronary events.[24] The relative risk associated with coronary calcification is similar to that associated with established factors such as smoking, hypertension, and diabetes mellitus. Progression of coronary artery calcification is associated with a higher incidence of coronary events even in those people who are asymptomatic at the time of initial scanning.[25] Thus, the presence of coronary artery calcification is not only indicative of atheromatous plaque disease, but also its progression may correspond with cardiovascular event rates. There are scarce data on the additive prognostic information

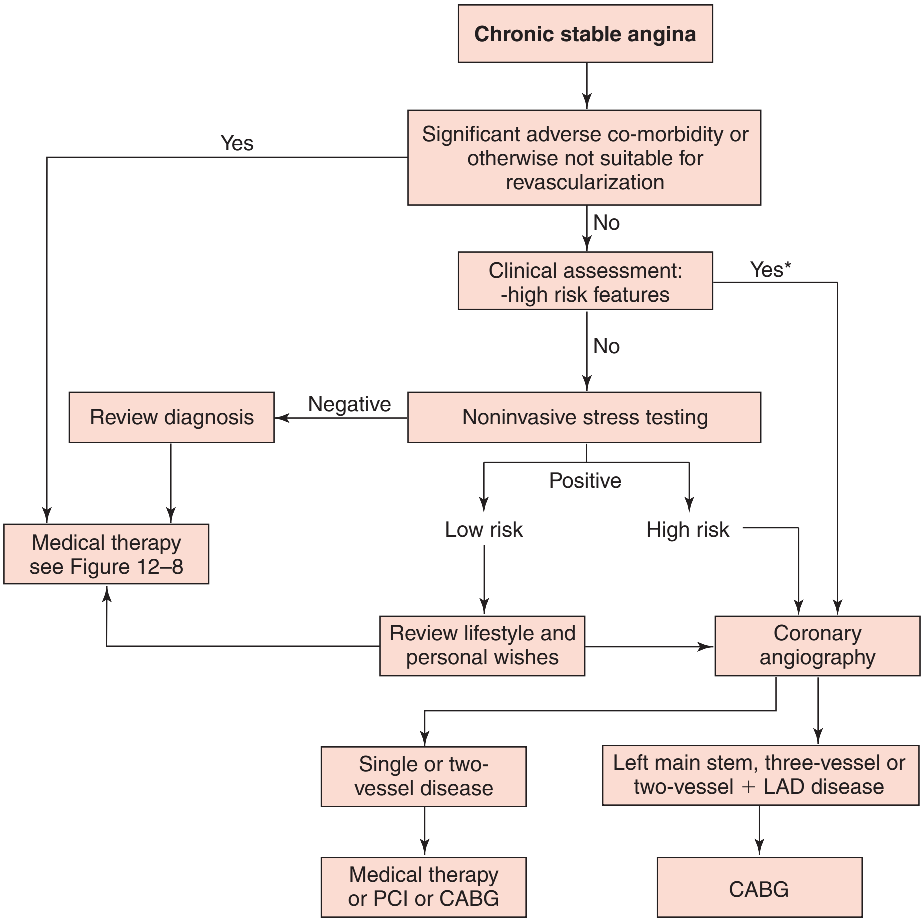


Figure 12–6 Schema for the management and treatment of patients with chronic stable angina. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LAD, left anterior descending coronary artery. *Many patients with high-risk clinical features will also require noninvasive testing to further aid risk stratification.

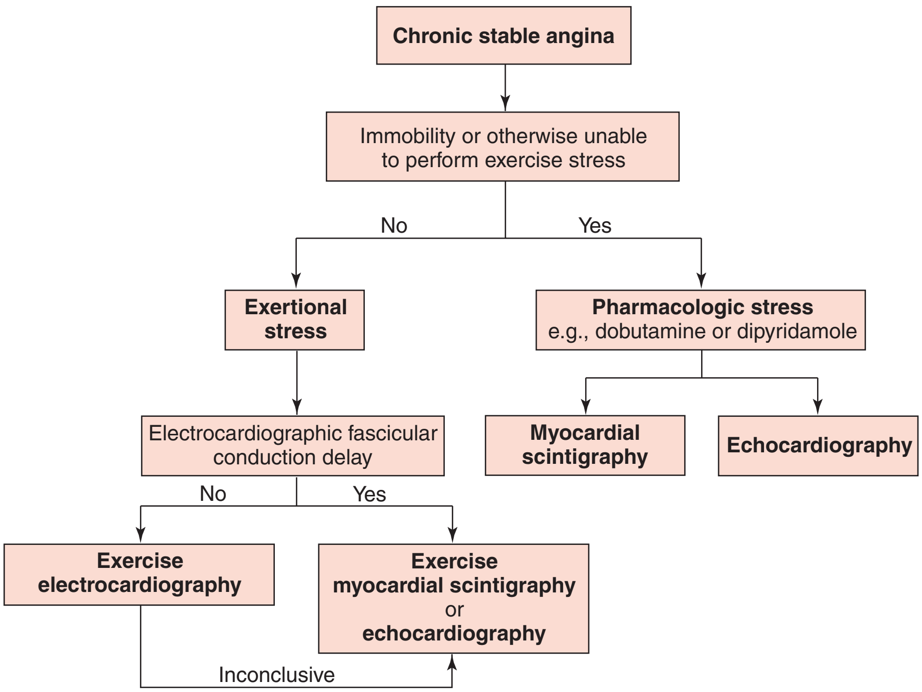


Figure 12–7 Schema for the selection of noninvasive stress testing for patients with chronic stable angina.

Table 12–6 Relative Advantages and Disadvantages of Three Main Noninvasive Stress Testing Methods

	Electrocardiography	Myocardial Perfusion Scintigraphy	Echocardiography
Technical difficulty	+	++	+++
Ease of interpretation	+	++	+++
Diagnostic sensitivity	50-80%	65-90%	65-90%
Diagnostic specificity	80-95%	90-95%	90-95%
Risk stratification	++	++	++
Identification of hibernating myocardium	–	++	+++
Identification of ischemic territory	+	++	++
Limitations	Intraventricular conduction defects and repolarization abnormalities	Radiation exposure	Limited value in patients with poor image quality
Cost	+	+++	++

in patients with stable angina, and its role is currently undefined. The ability of multidetector computed tomography scanners to reliably quantify coronary stenoses has yet to be achieved[26] but remains a promising future prospect.

Invasive Evaluation

Coronary angiography is used to aid the diagnosis and management of known or suspected coronary heart disease and is considered when either medical therapy has failed to provide effective symptomatic control or clinical and noninvasive tests suggest that the patient may be at high risk or may otherwise benefit prognostically from intervention.

Overall Assessment of Risk

A number of scoring systems[7,14,15,27-29] have been developed that incorporate both clinical characteristics and noninvasive investigations in the determination of risk. These models provide a more comprehensive assessment of risk and prognosis in patients with stable angina. Coronary angiography is appropriate in patients whose clinical characteristics or noninvasive investigations suggest they have an adverse prognosis and may therefore benefit prognostically from coronary artery bypass graft surgery (CABG) (Table 12–7; see Fig. 12–6).

The hazards of any intervention are more likely to outweigh the potential symptomatic and prognostic benefits in patients at low risk. In contrast, patients at high risk have the most to gain from interventions such as revascularization. Risk stratification is, therefore, an essential part of the initial assessment of a patient with stable angina. The main determinants of risk are patient characteristics such as age, diabetes mellitus, hypertension, and the results of clinical investigations such as exercise or other forms of stress testing, the extent of coronary disease (the number and type of vessels affected), and left ventricular function (see Figs. 12–1 to 12–3).

Table 12–7 Indications for Coronary Angiography

Severe or disabling angina. The severity of symptoms indicating the need for coronary angiography will vary depending on the patient's (and physician's) perception of the illness. However, most experts agree that patients with symptoms in Canadian Cardiovascular Society class 3 or 4, despite optimal medical therapy, may therefore benefit symptomatically from coronary artery bypass graft surgery or percutaneous coronary intervention.

Clinical indicators and noninvasive testing suggestive of adverse prognosis.

Continuing chest pain with inconclusive or negative noninvasive tests. In this context, a normal coronary angiogram can be very helpful in excluding obstructive coronary artery disease, removing uncertainty about the diagnosis, reassuring the patient, and thereby reducing their use of health care resources. This will be of particular concern when the symptoms limit the lifestyle of the patient or a diagnosis of coronary artery disease will have occupational ramifications.

THERAPEUTIC INTERVENTIONS

The treatment of patients with chronic stable angina pectoris should be directed toward both the alleviation of symptoms and an improvement in prognosis. This involves several approaches including lifestyle modification, management of risk factors, pharmacologic therapy, and coronary revascularization. All forms of intervention present certain hazards and should be instituted only if the perceived benefits, in terms of improved symptoms and prognosis, are likely to outweigh the associated risks. Such judgments are best made in the context of an overall treatment strategy that seeks to minimize the impact of the disease throughout the remainder of the patient's life. Figures 12–4 and 12–6 to 12–9 provide a general guide to the initial investigation and management of patients with chronic stable angina.

Lifestyle and Risk Factor Modifications

Lifestyle and risk factor modifications are integral parts of, and complementary to, the treatment of patients with chronic stable angina, because they may provide both symptomatic

and prognostic benefits. The benefits of exercise and exercise programs and the management of hyperlipidemia are discussed later. (The treatment and management of hypertension are discussed in Chapter 30.)

Smoking

Cigarette smoking is a major risk factor for the development of fatal and nonfatal MI.[30] Cessation of smoking is associated with major benefits, and repeated brief and supportive advice should be given to all patients.[31,32] Short-term nicotine replacement therapy should be offered to those individuals with a heavy consumption of tobacco (more than 10 cigarettes per day), because it is associated with up to a nine-fold increased likelihood of success.[33,34] The antidepressants bupropion and nortriptyline also aid long-term smoking cessation, but selective serotonin reuptake inhibitors such as fluoxetine do not.[35] This suggests that these agents produce their beneficial effects independent of an antidepressant effect. However, there appears to be no specific or effective treatment strategy to avoid relapse in smokers who have successfully quit for a short time.[36]

Dietary Intervention

Dietary intervention clearly complements the use of lipid-lowering therapy. Although a low-fat diet reduces serum cholesterol concentrations by an average of only 5%[37] even in motivated individuals,[38] dietary modification may provide additional preventive benefits, such as those obtained from a Mediterranean-type diet[39] or those high in (n-3) polyunsaturated fatty acids of fish oils.[40,41] Observational studies[42,43] and randomized trials[44] have suggested that the consumption of fruits and vegetables containing high levels of antioxidant vitamins, or supplementation with vitamin E,[45,46] is protective against the development of coronary events. However, three large-scale (n = 6000 to 30,000) multicenter randomized controlled trials[41,47,48] demonstrated that low- or high-dose vitamin E supplementation has no effect on cardiovascular outcomes. Modest alcohol consumption is associated with a reduced risk of coronary heart disease and should be limited to 21 to 28 units/week (1 unit = 8 g of absolute alcohol) for a man and 14 to 21 units/week for a woman.[49]

Obesity

There is a significant and independent association between body mass index and the risk of cardiovascular events.[50] Despite the high prevalence of obesity, there have been no interventional trials to show that weight reduction in obese patients with chronic stable angina or coronary artery disease improves symptoms or outcome. However, it is reasonable to assume that weight reduction would reduce the frequency of anginal episodes and potentially improve prognosis.

Currently escalating levels of obesity, particularly in Western societies, are associated with the development of the so-called "metabolic syndrome" characterized by obesity, insulin resistance, hypertension, and dyslipidemia. This has raised concerns about the incidence and prevalence of cardiovascular disease in the future. However, there are novel therapeutic strategies that may be able to reduce obesity and the metabolic syndrome. Cannabinoid type-1 receptor antagonism, when combined with a low-calorie diet, markedly enhances weight loss and improves many of the associated cardiovascular risk factors.[51] Its role in obese patients with coronary heart disease has yet to be established.

Diabetes Mellitus

Good glycemic control is essential in all patients with diabetes mellitus because of the reduced risk of long-term complications, including coronary artery disease. Although there are no specific trials of diabetic control in patients with chronic stable angina, primary prevention trials[52,53] and secondary prevention trials in patients after MI[54] indicate that cardiovascular morbidity and mortality rates are reduced with intensive hypoglycemic therapy regimens. Moreover, poor glycemic control at the time of presentation with MI is a poor prognostic sign.[55] Although previous studies[56] had suggested that sulfonylureas, in particular, tolbutamide, are associated with an increased risk of cardiovascular death, this was not confirmed in the U.K. Prospective Diabetes Study [UKPDS] trial.[57] The latter trial did, however, suggest that metformin should be the first-line agent of choice in overweight patients with diabetes mellitus because it is associated with a decreased risk of diabetes-related endpoints, less weight gain, and fewer hypoglycemic episodes.

Symptomatic Therapy

Cardiac Rehabilitation

Cardiac rehabilitation involves a multidisciplinary approach that addresses needs related to medical and psychosocial care, including exercise, education, secondary prevention, and vocational advice.[58] Although predominantly applied to the immediate post-MI or postoperative (after CABG) period, it is equally applicable to patients with chronic stable angina. The rehabilitation process encompasses the following three main components:

1. Explanation and understanding
2. Specific intervention, such as secondary prevention, exercise training, and psychological support
3. Long-term adaptation and education

Patients with stable angina who attend a regular exercise and rehabilitation program have less angina and may have fewer recurrent MIs, as well as better cardiorespiratory fitness and vocational status.[59,60] Exercise programs improve patient confidence and functional capacity, and although they are labor intensive, they are an efficacious and potentially cost-effective approach to the treatment of patients with stable angina (see Chapter 49).[61] Indeed, a contemporary randomized controlled trial suggested that an exercise program produced a better improvement in exercise capacity, was associated with fewer adverse cardiac events, and was more cost-effective than percutaneous coronary intervention.[62]

Pharmacologic Therapy

No single class of drug has been shown to be superior to another in the reduction of anginal episodes. However, because of the inferred secondary preventive benefits, β-blockers should be the first-line agents of choice (Fig. 12–8). Moreover,

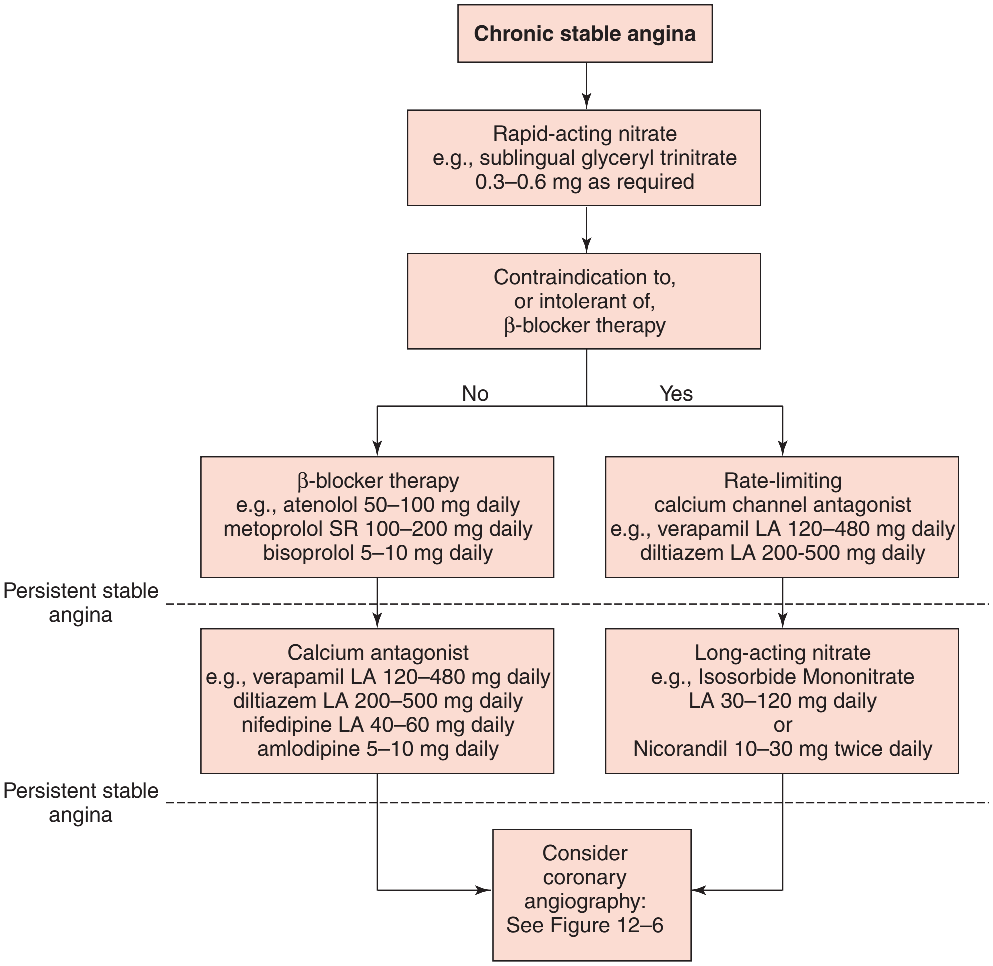


Figure 12–8 Schema for the symptomatic medical therapy management of patients with chronic stable angina. *Note:* the specific drug and dosage recommendations shown are not arranged in preferred sequence based on clinical trials and are not meant to exclude other drugs within the same class. Instead, they should be interpreted as examples of therapeutic suggestions based on the experience of the authors.

a meta-analysis suggests that β-blockers are better tolerated and may be more efficacious than calcium channel blockers in the treatment of chronic stable angina.[63]

If monotherapy does not control anginal symptoms, the introduction of a second antianginal agent provides significant but modest additional benefits (Figs. 12–8 and 12–9). The combination of β-blockade and rate-limiting calcium channel blockade may cause excessive bradycardia or heart block (see Fig. 12–8). However, this interaction is uncommon, and if there is concern, a long-acting dihydropyridine-type calcium channel blocker should also be prescribed. There is no definitive evidence that triple or quadruple antianginal therapy produces further benefit beyond dual therapy. Two large-scale (n = 5126, and 7665) randomized controlled trials of the addition of nicorandil[6] or nifedipine[5] to one or more antianginal (predominantly β-blocker) therapies demonstrated no major change in anginal symptoms, although nifedipine use was associated with a modest reduction in the need for coronary angiography (absolute reduction of 1.23% per year) and coronary artery bypass surgery (absolute reduction of 0.44% per year). Once daily and sustained-release preparations should be used whenever possible to aid compliance.

β-Blockers

β-Blockers inhibit the β-adrenergic receptors of the myocardium to produce negative chronotropism and negative inotropism of the heart. The attenuation of the heart rate response to exercise and stress reduces the myocardial oxygen demand and severity of ischemia. It also prolongs diastole, a major determinant of myocardial perfusion time. Randomized controlled trials[64,65] have demonstrated that β-blocker therapy is efficacious in reducing symptoms of angina and episodes of ischemia and in improving exercise capacity.

There is no evidence to support the suggestion that one type of β-blocker is superior to another. The so-called highly selective β-blockers, such as celiprolol or bisoprolol, or those with combined vasodilation and antioxidant properties, such as carvedilol, have no proven benefits above conventional β-blockers, such as atenolol or metoprolol. However, the secondary preventive benefits of β-blockers may be lost where agents have intrinsic sympathomimetic action,[66] and the use of such agents should, therefore, be avoided.

True side effects from β-blocker therapy are uncommon (less than 10%) but include symptoms, such as fatigue and lethargy, common complaints encountered on routine inquiry. A causative association should be established before permanent discontinuation of β-blocker therapy. Because of β-adrenergic receptor upregulation in the presence of β-blockade, patients should not be rapidly withdrawn from therapy. This can cause an acute withdrawal syndrome, and there is a suggestion that this may even precipitate acute MI.[67]

Calcium Channel Blockers

Patients who are intolerant of a β-blocker should be prescribed a rate-limiting calcium channel blocker such as diltiazem or verapamil. In the Danish Verapamil Infarction

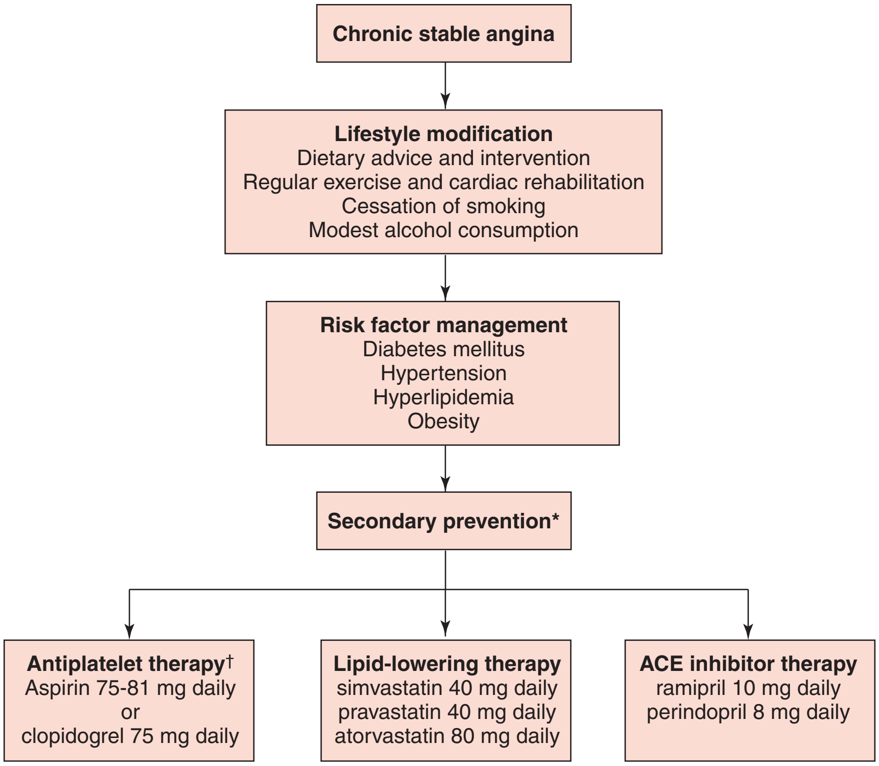


Figure 12–9 Schema for secondary prevention in patients with chronic stable angina. *If the patient is high risk, consider coronary angiography if the patient is suitable for revascularization. †Aspirin is preferred over clopidogrel as antiplatelet monotherapy. In patients who have undergone stent implantation, dual antiplatelet therapy is prescribed. See text for further discussion. *Note:* the specific drug and dosage recommendations shown are not arranged in preferred sequence based on clinical trials and are not meant to exclude other drugs within the same class. Instead, they should be interpreted as examples of therapeutic suggestions based on the experience of the authors.

Trial [DAVIT] II trial, a post-hoc analysis suggested that verapamil may be beneficial after MI in the absence of heart failure.[68] However, other calcium channel blockers[69] and classes of antianginal agents[70-72] are equally effective in relieving symptoms. The addition of nifedipine to other antianginal therapies does appear to reduce the need for further invasive investigation and revascularization.[5]

There is controversy as to whether calcium channel blockers can be used safely in patients with heart failure.[73] However, amlodipine has been shown to have a neutral effect on mortality rates in patients with heart failure and is an appropriate choice in patients with angina and significant left ventricular dysfunction.[74]

Nitrates

Nitrates were the first form of antianginal drug therapy to be discovered and used. Their mechanism of action is exerted through the release of nitric oxide either indirectly (glyceryl trinitrate) by reactions with sulfhydryl groups, such as methionine or cysteine, or directly (sodium nitroprusside) by interaction with plasma or cell membranes. The liberated nitric oxide causes endothelium-independent relaxation of vascular smooth muscle by increasing intracellular cyclic guanidine monophosphate (see Chapter 5).

Randomized controlled trials[70,75] demonstrated that nitrates are effective in reducing the frequency of anginal symptoms and in improving exercise capacity. However, as with calcium channel blockers, their use in severe aortic stenosis and hypertrophic obstructive cardiomyopathy should be avoided because of the potential to compromise coronary perfusion through peripheral vasodilatation and systemic arterial hypotension.

Acute relief of angina. Sublingual or buccal nitrates produce rapid and effective relief of acute anginal episodes. All patients should be provided with a sublingual nitrate preparation. Buccal preparations provide a more protracted release of nitrate, which is appropriate for prolonged activities that may provoke episodes of angina.

Prevention of anginal episodes. Long-acting nitrates, either oral or transdermal, provide effective relief of angina. Nitrates undergo extensive first-pass metabolism through hepatic glutathione reductases. However, topical and transdermal nitrate preparations are able to bypass such metabolism, and consequently, the overall dosage that is administered can be reduced. Alternatively, some nitrate preparations, such as isosorbide mononitrate, undergo less extensive hepatic metabolism and have better bioavailability and more prolonged action.

One of the main limitations of prophylactic nitrate use is the development of tolerance (see Chapter 5). This phenomenon requires a daily nitrate-free period,[76,77] usually nocturnal, to prevent the loss of efficacy and is a problem with all of the established nitrate preparations. The mechanism of nitrate tolerance development appears, at least in part, to be due to the depletion of sulfhydryl groups.[78] The development of *S*-nitroso-thiols potentially heralds a novel class of nitrates that may be devoid of nitrate tolerance[79] and have additional antiplatelet actions.[80]

Potassium Channel Agonists

This class of antianginal agents has vasodilatory and potential cardioprotective actions. Potassium channel openers act on the ion channels of the vascular smooth muscle cell and cardiac myocyte. Consequently, they may have a role in enhancing ischemic preconditioning[81] and improving the myocardial response to an ischemic insult.[82]

Nicorandil is the only preparation of this class in clinical use. It is effective in the treatment of angina and has both nitrate and potassium channel-opening properties. However,

there is no evidence that potassium channel openers are superior to other classes of antianginal agents, and their addition to preexisting antianginal therapy does not appear to improve symptoms.[6] The Impact of Nicorandil in Angina [IONA] trial[6] in 5126 patients with stable angina did demonstrate that nicorandil 20 mg twice daily was associated with modest 17% relative risk reduction in its primary endpoint of coronary heart disease death, nonfatal myocardial infarction, or unplanned hospitalization. The trial failed to demonstrate a difference in the secondary endpoint of coronary heart disease death and myocardial infarction.

Coronary Revascularization

Both CABG and percutaneous coronary intervention (PCI) carry measurable early morbidity and mortality risks that exceeds the early risks of medical therapy. As indicated, all interventions should be instituted only if the perceived benefits, in terms of improved symptoms and prognosis, are likely to outweigh the associated risks. This is particularly important when the therapy is targeted at symptomatic rather than prognostic benefits, such as with PCI or CABG for one-vessel disease.

Selection of the appropriateness and the type of revascularization procedure will be heavily influenced by technical aspects of the coronary anatomy, as well as by factors such as comorbidity and patient preference. What is considered to be an acceptable level of symptoms, optimal medical therapy, and tolerable drug side effects may vary greatly from patient to patient. Thus, the need for, and type of, coronary revascularization should take into account both objective clinical criteria and the patient's symptoms (see Chapter 8).

Several factors must also be considered when evaluating the applicability and evidence of the clinical usefulness of coronary revascularization strategies. First, the major randomized trials are based on highly selected patient groups and may not reflect the broad mix of patients who present to the clinic. For example, the Angioplasty Compared with MEdicine [ACME] trial[83] recruited only 212 patients out of the nearly 5000 who were screened. Second, most trials have not exclusively selected patients with chronic stable angina pectoris. Third, many datasets reported in the literature are outdated. Medical therapy has improved and become more effective. Similarly, the surgical results do not take account of the improvements in techniques and the increasing use of arterial conduits (Fig. 12–10). Indeed, the initial failure and restenosis rate in PCI has been reduced by the introduction of coronary artery stent deployment (Fig. 12–11), drug-eluting stents, and adjuvant therapy with antiplatelet agents.[84]

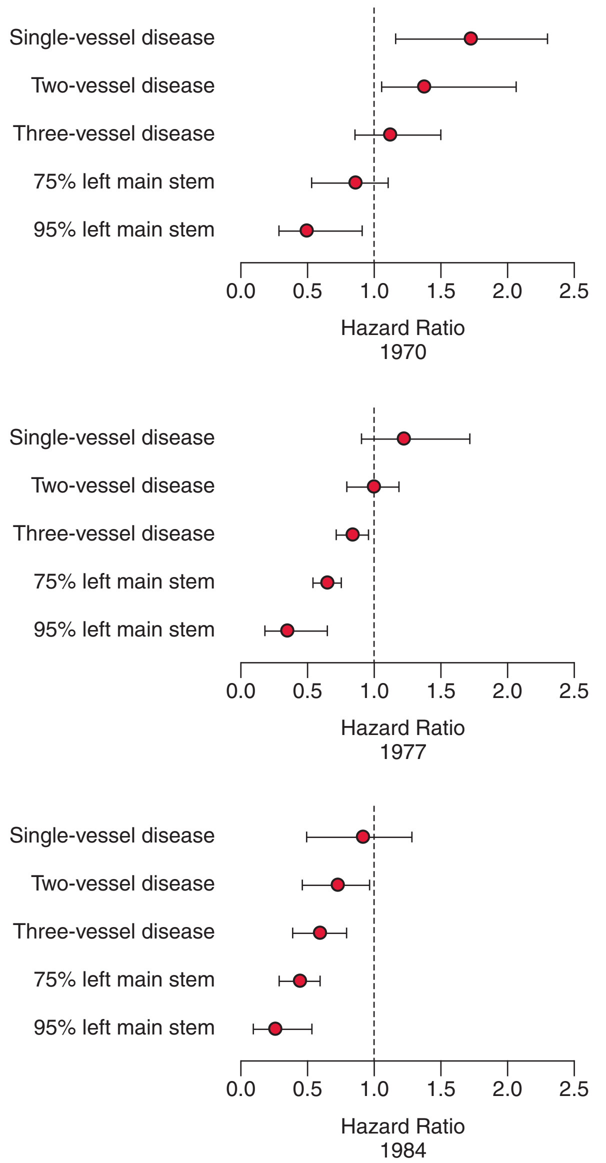


Figure 12–10 Improvements in survival with coronary artery bypass graft surgery (to left of vertical dashed lines) during a 14-year period. (Data from Califf RM, Harrell FE, Lee KL, et al: The evolution of medical and surgical therapy for coronary artery disease: a 15-year perspective. JAMA 1989;261:2077.)

Percutaneous Coronary Intervention

Complications

The most common serious complication of PCI is acute occlusion of the dilated vessel due to dissection or thrombosis. Other complications include vascular damage; thromboembolism, including stroke; and hemorrhage due to anticoagulant therapy. Although the risks are greatest with acute coronary syndromes,[85,86] elective percutaneous coronary intervention is associated with overall angiographic success rates of 96% to 99%, with transmural myocardial infarction rates of 1% to 3%, emergency coronary bypass surgery rates of 0.2% to 3%, and unadjusted in-hospital mortality rates of 0.5% to 1.4%.[87]

The reported risk of angiographic restenosis for isolated balloon angioplasty is 25% to 40%.[88-91] Restenosis occurs predominantly within the first 3 to 6 months,[89,90] does not always lead to recurrent symptoms, and has been dramatically reduced by the widespread use of intracoronary stents,[88,92-96] particularly drug-eluting stents. Current rates of restenosis with drug-eluting stents are 5% to 10%.[97]

The success and complication rate of PCI are influenced by many factors, including age, gender, clinical presentation, left ventricular function, comorbidity (e.g., diabetes mellitus), and the experience of the operator.[86,98] However, the most important determinant of outcome is the nature of the target

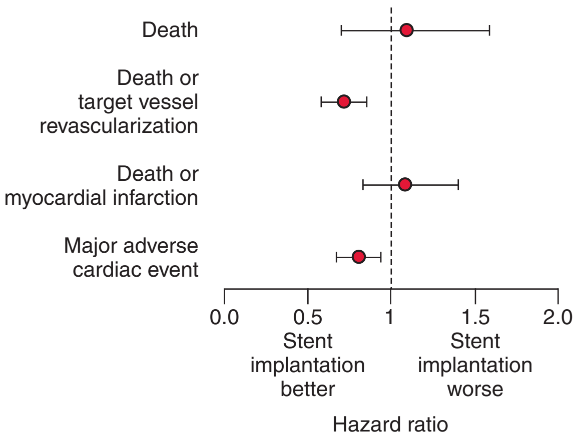


Figure 12–11 Improvements in 1-year clinical outcome with the introduction of coronary stenting. (Data from Rankin JM, Spinelli JJ, Carere RG, et al: Improved clinical outcome after widespread use of coronary artery stenting in Canada. N Engl J Med 1999;341:1957.)

lesion. A short, discrete, soft lesion on a straight segment of artery that does not compromise a major branch is ideal for PCI. Lesions that are less suitable for PCI include chronic total occlusions, long lesions, calcifications, lesions that lie on tortuous segments or flexures, and lesions that involve branch vessels. PCI has a high success rate and low complication rate for ideal lesions but a low success rate and high complication rate for complex lesions.

Indications: PCI versus Medical Treatment

The first randomized controlled trial to assess the usefulness of PCI in comparison with medical therapy was the ACME trial.[83] This study recruited patients with one-vessel disease, the majority of whom (>90%) had stable angina pectoris, and demonstrated that PCI is associated with superior subjective and objective improvements in anginal symptoms at 6 months.[83,99] However, there was concern that PCI was associated with a higher incidence of complications, particularly recurrent revascularization procedures.

The subsequent Randomised Intervention Treatment of Angina [RITA-2] trial[100] was a larger (n = 1018) and more powerful randomized controlled trial that was designed to compare the effects of PCI with medical therapy in patients with angina and one-vessel (60%) or multivessel (40%) disease. The study population did, however, include patients who had quiescent angina with no symptoms (20%) or recent (7 to 90 days before randomization) unstable angina (10%). Consistent with the ACME trial,[83] an initial strategy of PCI was associated with significantly less angina for at least 2 years after the procedure compared with medical treatment. This reduction in anginal symptoms was associated with a diminished requirement for antianginal drug therapy, an increase in exercise capacity, and an overall improvement in quality of life.[100,101] However, reflecting the low-risk population of patients recruited into this trial, PCI was associated with nearly twice the risk of death or nonfatal MI (6.3% versus 3.3% at 2.7 years, $P = 0.02$), which occurred predominantly in the first 3 months after randomization. It should also be noted that one fourth of patients randomized to medical treatment required a revascularization procedure during follow-up owing to worsening symptoms.

The symptomatic benefits of PCI in the RITA-2 trial[100] appeared to be most marked in the patients with severe symptoms or limited exercise tolerance. It may, therefore, be necessary to accept a small initial procedure-related hazard from PCI to gain relief from severe or limiting anginal symptoms. However, improved imaging and stent technologies combined with better antiplatelet therapies, such as the thienopyridines and glycoprotein IIb/IIIa receptor antagonists, mean that the hazards identified in RITA-2[100] have been overestimated in the current era. Thus, PCI is an appropriate intervention in chronic stable angina patients with suitable coronary anatomy who have chronic stable angina with limiting symptoms despite medical treatment (see Fig. 12–6).

PCI versus CABG

A meta-analysis[102] of eight large randomized controlled trials that compared PCI (n = 1710) with CABG (n = 1661) in patients with predominantly stable angina (80%) has shown no significant difference in survival between the two revascularization strategies during a mean follow-up of 2.7 years. There is, however, a significant difference in the subsequent need for additional revascularization, with 17.8% of patients randomized to PCI requiring CABG within 1 year and about 2% per year requiring CABG in subsequent years. The prevalence of angina at 1 year was considerably higher in the PCI group (1.5- to 2-fold), but at 3 years, this difference was no longer significant.[102]

The Bypass Angioplasty Revascularization Investigation [BARI] trial[103] was published after the meta-analysis by Pocock and colleagues[102] and is the largest study to compare PCI with CABG, although only 40% of patients recruited into this trial had stable angina. This trial also showed no significant difference in survival or risk of MI between PCI and CABG patients; however, PCI was again associated with a higher rate of subsequent revascularization procedures (8% for CABG versus 54% for PCI at 5 years). This excess of additional procedures for PCI was again seen predominantly in the first year. However, in the Arterial Revascularisation Therapy Study [ARTS][104] and Stent or Surgery [SOS, 2002] trials,[105] the introduction of elective coronary artery stenting reduced the apparent need for recurrent revascularization procedures in patients with multivessel disease (4% to 6% for CABG versus 17% to 21% for PCI at 1 to 2 years). The further impact of drug-eluting stents on recurrent revascularization procedures after PCI has not been assessed in comparison with a strategy of CABG.

The Duke University data base (n = 9263) describes a single-center prospective experience of the outcomes in patients with ischemic heart disease (20% of patients had stable angina) who were managed with medical therapy, PCI, or CABG. These data suggested that patients with one-vessel disease or two-vessel disease without involvement of the proximal left anterior descending coronary artery (LAD) experience better clinical outcomes with PCI than with CABG.[106,107] This contrasts with the findings of the Pocock and colleagues[102] meta-analysis, where the combined endpoint of death or MI in one-vessel disease appeared to be less frequent with CABG than with PCI (4.5% versus 7.2%). However, the subgroup analysis reported by Pocock and colleagues encompassed only

three trials with small numbers ($n = 350$ for each group), and the authors question the reliability of the finding.[106] In contrast to the Duke University data base, the patients in these randomized trials were highly selected populations: for example, the RITA trial[108] recruited only 3% of patients undergoing an angiogram.

Therefore, it would appear that PCI is an appropriate alternative to CABG in patients with symptom-limiting chronic stable angina despite medical treatment who have suitable one-vessel disease or two-vessel disease without a significant proximal LAD stenosis.

Culprit Lesion PCI

When the main objective of revascularization is the relief of angina, it may be advisable to consider PCI of the lesion that is believed to be responsible for the patient's symptoms, even if there is evidence of multivessel disease that might otherwise be treated with CABG. This strategy, known as culprit lesion PCI, is often appropriate in symptomatic patients with multivessel coronary artery disease who have a single exceptionally severe stenosis and many minor lesions or in those patients who are unsuitable for CABG owing to comorbid conditions such as cerebrovascular disease or chronic obstructive airway disease.[109] Culprit lesion PCI is also a reasonable option in situations where surgical revascularization with CABG would be incomplete and, therefore, may not confer prognostic benefit.

PCI After CABG

Five years after undergoing CABG, 50% of patients will have redeveloped angina,[23] and by 12 years, 30% will have undergone repeat revascularization.[110] Repeat CABG is associated with a higher risk and a lower likelihood of benefit than the initial intervention. In an analysis of 632 nonrandomized patients with previous CABG who required either elective repeat CABG or PCI, complete revascularization was achieved in 38% of patients who underwent PCI compared with 92% of patients who underwent CABG. However, complications were significantly lower with PCI (0.3% versus 7.3%), and survival was similar at 1 and 6 years of follow-up. Both procedures resulted in similar event-free survival from death, MI, and angina, but by 6 years, further revascularization with either repeat PCI or CABG was significantly higher with PCI (64% versus 8%).[111]

These findings were confirmed in a larger cohort of 4174 patients who underwent coronary revascularization (nonrandomized PCI or CABG) after previous CABG.[112] Repeat CABG was associated with a higher in-hospital mortality rate (6.8%) than PCI (1.2%), but mortality rates were similar at 1, 5, and 10 years. PCI was again associated with an increased risk of recurrent angina and additional procedures.

When technically feasible, we prefer an initial strategy of PCI rather than repeat CABG in chronic stable angina patients with limiting angina despite previous CABG and medical therapy.

Stents

Intracoronary stents were initially used for the management of serious complications arising from PCI such as acute or threatened vessel occlusion, so-called *bail-out stent implantation*. This provided an extremely useful way of maintaining vessel patency and led to a reduction in the need for emergency CABG after PCI.[113] Observational studies[96,113-115] and initial randomized controlled trials have confirmed the clear usefulness of the technique in the management of acute vessel closure.

Several randomized controlled trials assessed the efficacy of elective intracoronary stenting. Some of the studies have methodologic limitations such as control patients who did not receive matched anticoagulation regimens (the STent REStenosis Study [STRESS] trial)[88] or investigators who were not fully blinded (the BElgian NEtherlands STENT [BENESTENT] and Stenting In Chronic Coronary Occlusion [SICCO] trials).[92,116,117] However, all trials report consistent findings, with elective stenting being associated with improved procedural and clinical outcomes and a reduction in the need for subsequent revascularization procedures. The clearest evidence has come from PCI procedures for higher-risk lesions, namely chronically occluded arteries,[117-119] saphenous vein grafts,[120] proximal LAD stenoses,[95] and restenosis after prior PCI.[121,122] Stent implantation is also appropriate when conventional PCI has produced a suboptimal result.[93]

In the BENESTENT study,[92] the effect of elective stenting of all lesions was compared with the use of PCI alone in patients with stable angina and a single new lesion. There were no procedure-related deaths in this trial, and stenting was associated with improved clinical and angiographic outcomes. The subsequent BENESTENT II study[123] included patients with unstable angina (40%) and was able to confirm the benefits of elective stent implantation using heparin-coated stents. However, a more selective approach of stent implantation for high-risk lesions or suboptimal angiographic results may confer similar benefits and be more appropriate.[124]

Observational studies[96,113,125] and randomized controlled trials[88,92,116,126] indicate that after stent implantation, patients have less restenosis and greater event-free survival from MI and repeated coronary intervention. Subsequent to the widespread use of stents in Canada, evidence of improved clinical outcome, particularly a reduced need for recurrent coronary intervention, was observed (see Fig. 12–11).[96]

Coated stents have become available wherein agents are impregnated into a polymer coating (see Chapter 7). One of the first to be employed was a heparin-coated stent. This was used to reduce the incidence of stent thrombosis and restenosis. However, these heparin-coated stents had limited benefits above bare metal stents. There has been major interest in the use of drug-eluting stents that contain antiproliferative agents. Sirolimus is a macrolide antibiotic with antifungal, immunosuppressive, and antimitotic properties that has been used in the prevention of renal transplant rejection. Sirolimus-coated stents are associated with a dramatic reduction in the incidence of in-stent restenosis, with failure of target vessel revascularization falling from 21.0% to 8.6% in the SIRIUS study of 1058 patients with coronary heart disease.[97] Paclitaxel is a microtubule-stabilizing agent with potent antitumor activity that has also been successfully used in stent coatings with similar reductions of in-stent restenosis.

Antiplatelet Therapy

All patients with coronary artery disease should be maintained on aspirin therapy (see later) (see Fig. 12–9).[127] Aspirin therapy is associated with a 53% reduction in the rate of vas-

cular occlusion after PCI (2.7% versus 5.5%).[127] The combination of ticlopidine (250 mg twice daily) and aspirin (100 mg twice daily) compared with conventional anticoagulant therapy reduces both cardiac events and the associated hemorrhagic and vascular complications after PCI and stent deployment.[128] Indeed, the combination of aspirin and ticlopidine is supe-rior to the use of aspirin either alone or in combination with warfarin.[129] Observational data[130] indicate that clopidogrel (75 mg/day) is as efficacious as ticlopidine in the prevention of stent thrombosis and is now the first-line agent of choice.[131]

More potent platelet antagonists have become available that inhibit the platelet glycoprotein IIb/IIIa receptors (see Chapters 5 and 10). A meta-analysis[132] of 16 randomized controlled trials incorporating 32,135 patients confirms the modest beneficial effects of platelet glycoprotein IIb/IIIa antagonists in patients during PCI or acute coronary syndromes. The ISAR-REACT trial has brought into question the role of glycoprotein IIb/IIIa receptor antagonists in elective percutaneous coronary intervention.[133] When all patients are pretreated with a large oral loading dose (600 mg) of clopidogrel, there appears to be no additional benefit of a glycoprotein IIb/IIIa receptor antagonist, although appropriately powered trials with a broad spectrum of patients at different degrees of risk of events need to be performed.

Coronary Artery Bypass Graft Surgery

Complications

When contemplating revascularization surgery in patients with chronic stable angina, it should be recalled that CABG is a safe operation with an elective surgical mortality rate frequently reported at around 2% to 4%, depending on the case mix.[134] Various factors influence surgical mortality rates, including age, gender, degree of left ventricular impairment, and the presence of other comorbid conditions, such as diabetes mellitus, obesity, and hypertension (Fig. 12–12).[134]

Indications. CABG Versus Medical Treatment

The three major randomized controlled trials that compared CABG with medical therapy are the Coronary Artery Surgery Study [CASS],[135] the Veterans Administration [VA] Cooperative Study,[11,136] and the European Coronary Surgery Study [ECSS].[12,137] These studies form the basis of the meta-analysis by Yusuf and colleagues[138] that compares CABG with medical therapy in patients with chronic stable angina.

In comparison with medical therapy, CABG significantly improves symptoms of angina and exercise capacity and reduces the need for antianginal therapy.[135] After CABG, more than 70% of patients are free of angina at 1 year and 50% are free at 5 years.[135,137] Patients experience a better quality of life after CABG[135,139,140] and report less limitation in physical activity.[135] Seventy-three percent of patients are working 1 year after CABG.[140]

Therefore, CABG is an appropriate intervention in patients who have suitable coronary anatomy with chronic stable and symptom-limiting angina despite medical treatment (see additional discussion in Chapter 8).

Arterial Conduits

As a consequence of graft vasculopathy, saphenous vein bypass grafts have an accelerated failure rate that is particularly evident beyond the fifth year. Arterial conduits are being used increasingly in an attempt to improve graft survival. The internal mammary arteries are the principal conduits to have been assessed, although other conduits, such as the radial and gastroepiploic arteries, may also be used (Chapter 8).

Fifteen years after CABG, 88% of left internal mammary artery grafts remain patent compared with only 32% of saphenous vein grafts.[141] Observational and quasi-experimental studies have shown that this improved patency rate is associated with better long-term survival rates and a reduction in the risk of angina, hospitalization, MI, and repeat operation.[142-144] Overall, patients who undergo CABG with saphenous vein

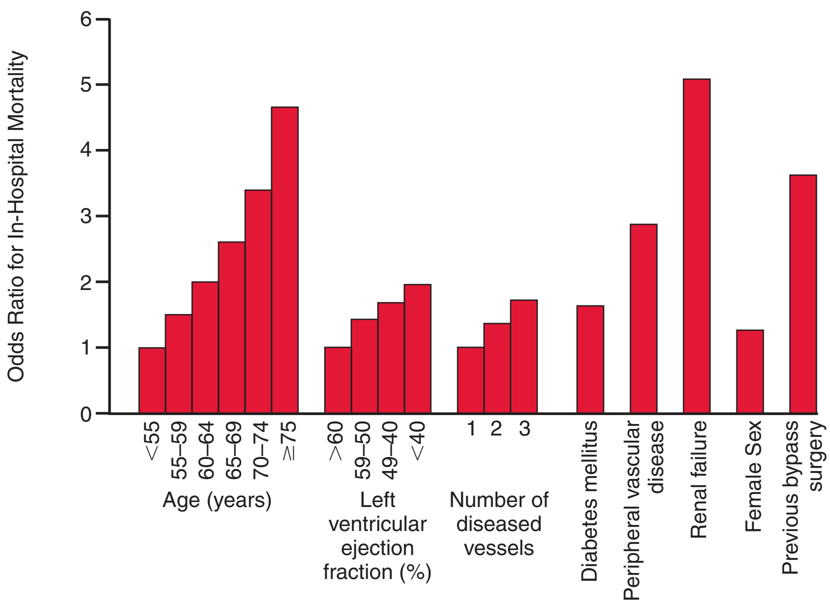


Figure 12–12 Odds ratio for in-hospital mortality rate for a selection of patient characteristics. Patients with chronic stable angina comprise 40% of the study population. (Data from O'Connor GT, Morton JR, Diehl MJ, for the Northern New England Cardiovascular Disease Study Group: Differences between men and women in hospital mortality associated with coronary artery bypass graft surgery. Circulation 1993;88:2104.)

grafts have only a 1.6-fold greater risk of death over 10 years compared with those who receive an internal mammary artery graft.[142] Given the chronic nature of ischemic heart disease, where technically feasible, CABG surgery should incorporate the use of arterial conduits such as one or both of the internal mammary arteries.

Secondary Prevention

Many approaches have been taken to improve the prognosis of patients with ischemic heart disease (see Fig. 12–9). Some therapeutic interventions are associated with marked benefits, whereas others remain unproven or have neutral effects (Fig. 12–13). However, as in the case of PCI, it may be necessary to accept a small initial risk to improve the patient's symptoms and quality of life. The side effects of therapy, such as angiotensin-converting enzyme (ACE) inhibitor-induced cough, may limit the use of agents with proven prognostic benefits.

Cardiac Rehabilitation

The majority of randomized controlled trials of cardiac rehabilitation have been conducted in patients who have sustained a recent MI and indicate that significant morbidity and mortality benefits can be achieved.[145] Although the benefits appear to be most prominent in the first 2 years, the secondary preventive effects appear to be sustained during a 10-year period.[146] Although these benefits have not been definitively demonstrated in populations of patients with chronic stable angina in the absence of MI, the referral of such patients to a cardiac rehabilitation program is appropriate (see Chapter 49).

Antiplatelet Therapy

Although aspirin is a weak inhibitor of platelet aggregation, it is a simple and effective treatment in patients with chronic stable angina. The Antithrombotic Trialists' Collaboration performed a meta-analysis that demonstrated a significant morbidity and mortality benefit (33% relative risk reduction) with long-term aspirin therapy in patients with chronic stable angina,[127] especially in those who have undergone coronary revascularization (Fig. 12–14).[127] Because of this proven reduction in the risk of death and MI, all patients with stable angina pectoris should be maintained on regular aspirin therapy. Similar benefits of aspirin therapy are seen at all doses of ≥75 mg daily whereas bleeding risks increase in a dose-dependent manner. It would appear that aspirin 75–81 mg daily is the preferred dose for long-term secondary prevention. If there is concern regarding the risk of peptic ulceration and gastrointestinal bleeding, then co-administration of a proton pump inhibitor is appropriate.[147]

The weak antiplatelet action of aspirin has led to the search for other, more potent antiplatelet agents (see Chapter 5). In the CAPRIE trial,[148] long-term clopidogrel treatment (75 mg/day) is at least as efficacious as aspirin in the preven-

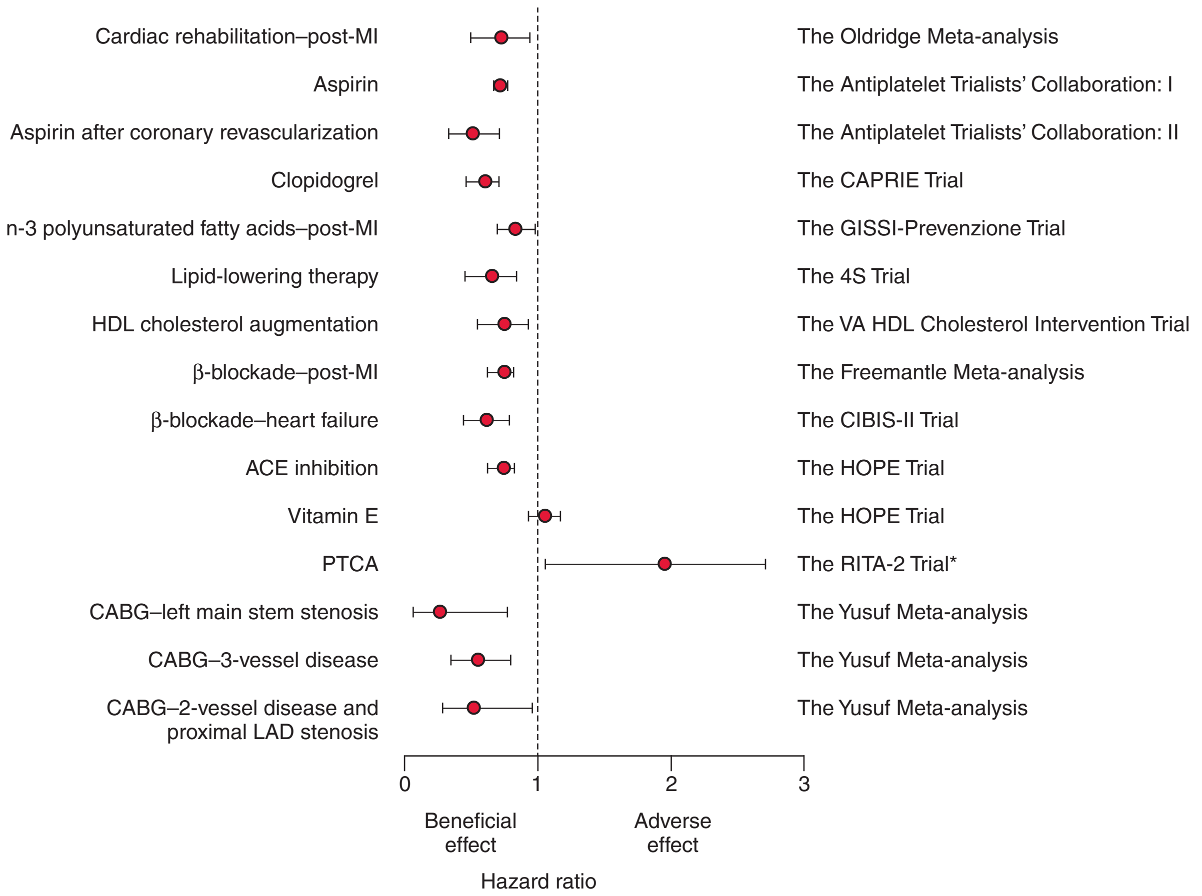


Figure 12–13 Proportionate benefits of a range of potential secondary preventive therapies. *The RITA-2 Trial predominantly recruited patients with a low cardiovascular risk. (From the RITA-2 Trial Participants: Coronary angioplasty versus medical therapy for angina: The second Randomized Intervention Treatment of Angina (RITA-2) Trial. Lancet 1997;350:461.)

tion of ischemic stroke, MI, or vascular death in patients with atherosclerotic vascular disease. Although the overall secondary preventive benefits of clopidogrel statistically exceeded those of aspirin, the relative benefits were modest (relative risk reduction, 8.7%; $P = 0.04$) and, due to significant study population heterogeneity ($P = 0.04$), may not confer superior benefit to aspirin in patients with stable ischemic heart disease. Clopidogrel is beneficial when used in combination with aspirin, in patients with acute UA/NSTEMI (see Chapter 10). Clopidogrel is indicated as an alternative to aspirin, particularly in patients with aspirin sensitivity. Combination aspirin and clopidogrel therapy is of minimal benefit in patients with chronic stable angina and cannot be recommended for long-term secondary prevention.

Potent platelet antagonists have become available that inhibit the final common pathway of platelet aggregation, the platelet glycoprotein IIb/IIIa receptor. Trials of oral non-peptidic antagonists of the IIb/IIIa receptor in patients with a recent acute coronary syndrome have been disappointing and were associated with an increase in mortality.[149,150] The role of such agents in patients with chronic stable angina has not been directly assessed, but they are unlikely to have significant secondary preventive benefits and may cause harm.

Lipid-Lowering Therapy

Serum cholesterol concentrations should be assessed in all patients with chronic stable angina to detect hypercholesterolemia and should be treated with a hydroxy-3-methyl glutaryl coenzyme A reductase inhibitor or "statin" irrespective of the serum cholesterol concentration (see Chapter 26). There have been several large-scale randomized controlled trials to address the issue of lipid-lowering therapy in patients with ischemic heart disease. The Scandinavian Simvastatin Survival Study [4S] trial[151] was the first to demonstrate a significant improvement (relative risk reduction, 30%) in mortality rates with the use of statins in patients with ischemic heart disease and a serum cholesterol concentration of more than 210 mg/dL (more than 5.5 mmol/L). These mortality benefits have been demonstrated with both simvastatin and pravastatin,[152] and the goal of therapy appears to be suppression of the serum total cholesterol concentration to at least below 190 mg/dL (below 5.0 mmol/L). The Cholesterol and Recurrent Events [CARE] study[152] has, in addition, suggested that patients with average cholesterol concentrations (low density lipoprotein [LDL] cholesterol, 120 to 150 mg/dL; 3.2 to 3.9 mmol/L) should also be considered for lipid-lowering therapy because it is associated with a similar 26% relative risk reduction in future adverse cardiac events. However, the absolute risk of a subsequent cardiac event is proportionately lower in patients with such normal concentrations, especially in patients with only chronic stable angina. In contrast, more aggressive lipid lowering appears to have substantial additional benefits in patients who have undergone saphenous vein bypass grafting,[153] and under such circumstances, target LDL cholesterol concentrations should be below 100 mg/dL (below 2.6 mmol/L).

The 4S trial[151] has been the only large-scale mortality study to specifically recruit patients with chronic stable angina. However, the benefits of lipid-lowering therapy in chronic stable angina were also demonstrated in the Atorvastatin VErsus Revascularization Treatment [AVERT] study.[154] During an 18-month follow-up period, this trial was able to demonstrate that in patients with chronic stable angina, atorvastatin reduced the number of acute ischemic

Category of trial	No of trials with data	No (%) of Vascular Events: Allocated antiplatelet	No (%) of Vascular Events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10,022 (17.0)	−159.8	567.6	25 (4)
Acute myocardial Infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	−181.5	519.2	30 (4)
Previous stroke/transient ischemic attack	21	2045/11,493 (17.8)	2464/11,527 (21.4)	−152.1	625.8	22 (4)
Acute stroke	7	1670/20,418 (8.2)	1858/20,403 (9.1)	−94.6	795.3	11 (3)
Coronary artery disease:						
Unstable angina	12	199/2497 (8.0)	336/2534 (13.3)	−64.8	104.6	46 (7)
Coronary artery bypass	25	149/3105 (4.8)	146/3126 (4.7)	−1.9	47.4	4 (14)
Coronary angioplasty	9	43/1592 (2.7)	89/1620 (5.5)	−18.7	24.6	53 (14)
Stable angina/coronary artery disease	7	144/1448 (9.9)	208/1472 (14.1)	−30.7	76.3	33 (9)
Heart failure	2	4/66 (6.1)	7/68 (10.3)	−1.0	1.9	41 (56)
Subtotal	55	539/8708 (6.2)	786/8820 (8.9)	−117.1	254.8	37 (5)
All trials	**195**	**7705/71,912 (10.7)**	**9502/72,139 (13.2)**	**−811.4**	**3244.9**	**22 (2)**

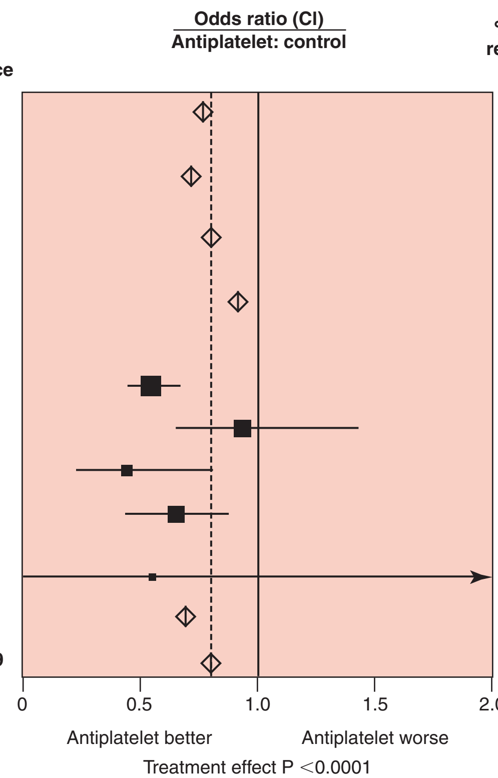


Figure 12–14 Benefits of aspirin therapy in patients with, or at risk of, cardiovascular disease. (Reproduced with permission from the Antithrombotic Trialists' Collaboration [BMJ 2002;324:71]).

events—hospitalization for worsening angina or coronary revascularization procedures—in comparison with intervention with PCI (13% versus 21%, respectively). However, PCI was associated with a greater improvement in chronic anginal symptoms than atorvastatin (54% versus 41%, respectively), and a large amount of the effect seen is likely to reflect the RITA-2 trial observations[100] that PCI improves chronic symptoms at the cost of a small but significant increase in short-term ischemic events.

In the initial secondary prevention trials, patients were predominantly recruited if serum total cholesterol concentrations were above a certain threshold—usually around 190 mg/dL. There appeared to be a threshold effect in the CARE trial[152] that suggested there was no merit in reducing serum LDL cholesterol concentrations to below 120 mg/dL. The subsequent Heart Protection Study[155] has now definitively established that all patients with coronary heart disease should receive statin therapy: it is the overall absolute risk that is important rather than the cholesterol concentration per se. If a patient is at high-risk, he or she will benefit from cholesterol reduction irrespective of their cholesterol concentration (i.e., there does *not* appear to be a threshold effect for the benefits of statin therapy). For example, in the Heart Protection Study,[155] patients with a total cholesterol concentration of less than 190 mg/dL had a 5-year event rate of 22.1% that was reduced to 16.9% by simvastatin 40 mg daily. Thus, a patient with chronic stable angina, diabetes mellitus, or peripheral vascular disease will merit having statin therapy even if his or her total cholesterol concentration is 136 mg/dL. A meta-analysis[156] of 14 major statin trials incorporating 90,056 individuals has reaffirmed these benefits and suggests that event reduction is proportional to LDL cholesterol reduction (Fig. 12–15).

How low should the serum cholesterol concentration be reduced in patients with chronic stable angina? The PROVE-IT[157] and TNT[158] trials have assessed, respectively, whether more intensive lipid-lowering therapy is associated with better outcomes in patients with recent unstable or chronic stable coronary heart disease. Both trials show a consistent benefit in reducing serum LDL cholesterol concentrations below contemporary guidelines (to a mean of 62 to 77 mg/dL). In the TNT trial,[158] 30 patients treated with atorvastatin 80 mg daily for 5 years will avoid 1 major cardiovascular event in comparison with those receiving atorvastatin 10 mg daily. The IDEAL trial compared atorvastatin 80 mg daily with simvastatin 20 mg daily as secondary prevention in patients with a previous MI.[158a] The achieved LDL cholesterol was 81 mg/dL compared with 104 mg/dL in the simvastatin group. The composite primary endpoint of coronary death, nonfatal MI, or resuscitated cardiac arrest tended to be lower in the high-dose atorvastatin group (HR 0.89; 0.78 to 1.01, $P = 0.07$); nonfatal MIs were significantly reduced with high-dose atorvastatin (HR 0.83; 0.71 to 0.98; $P = 0.02$) over a median follow-up of 4.8 years.

Other classes of drugs, such as fibrates, also lower serum lipid concentrations, but although it is inferred, they have not been shown clearly to reduce mortality rates in randomized controlled trials. One exception to this is the Veterans Affairs trial of gemfibrozil, which demonstrated significant secondary preventive benefits of elevating reduced high-density lipoprotein (HDL) cholesterol concentrations.[159] Patients with ischemic heart disease, including patients with chronic stable angina, and a normal LDL cholesterol concentration (140 mg/dL or less) but a reduced HDL cholesterol concentration (40 mg/dL or less) benefited from 1.2 g/day gemfibrozil, which elevated HDL cholesterol concentrations by 6% and reduced total cholesterol and triglyceride concentrations by 4% and 31%, respectively, without altering LDL cholesterol concentrations. Fibrates should, therefore, be considered in patients with normal LDL but low HDL cholesterol concentrations.

β-Blockers

There have been no randomized controlled trials to demonstrate that β-blocker therapy improves survival in patients with chronic stable angina. However, post-MI,[66,160] hypertension, and case-control[161] studies have shown that patients maintained on β-blockers are less likely to have a vascular event and have a reduced mortality rate if they subsequently experience an MI. For these reasons, we believe β-blockers should be the first-line agents of choice for patients with chronic stable angina. Furthermore, despite claims to the contrary, hypertension[162] and angina[63,65] trials indicate that β-blockers are better tolerated and have fewer side effects than calcium channel antagonists. Concerns that β-blocker therapy is associated with reduced peripheral perfusion, due to unopposed α-adrenergic vasoconstriction and blockade of β_2 vascular receptors, are unfounded,[163] even in patients with peripheral vascular disease. β-Blockers may have significant secondary preventive benefits in patients with peripheral vascular disease—as suggested by the marked reductions in perioperative mortality and MI rates in such patients undergoing major vascular surgery.[164]

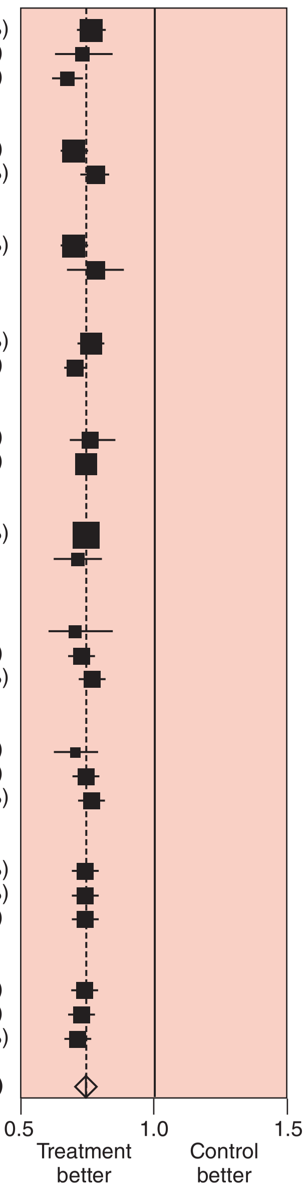
Because of the common risk factor of smoking, many patients with angina have chronic obstructive pulmonary disease and are denied β-blocker therapy owing to the concern of provoking bronchospasm. However, there is a large body of observation data demonstrating that patients with obstructive pulmonary disease derive similar mortality benefits (40% relative risk reduction) after MI with β-blocker therapy.[160] Therefore, such patients should be given a trial of β-blockade because the majority tolerate therapy well. If there is genuine concern of clinically significant reversible bronchospasm, formal spirometry in the presence and absence of a β_2-agonist, such as 5 mg nebulized salbutamol, should be performed.

Patients with chronic stable angina and coexistent heart failure are particularly at risk and should also be given β-blocker therapy as the agent of choice. There have been several large-scale randomized controlled trials that demonstrated major mortality and morbidity benefits in patients with mild to severe heart failure[165,166] who were maintained on β-blocker therapy. Although cautious dose up-titration and close clinical observation for cardiac decompensation are necessary, the withdrawal rates of patients with heart failure from β-blocker therapy are modest (15%) and equivalent to those for placebo.[166] Moreover, rates of rehospitalization are reduced and symptoms of heart failure are improved with β-blocker therapy.[166]

Angiotensin-Converting Enzyme Inhibition

The major morbidity and mortality benefits of ACE inhibitor therapy were first demonstrated in patients with heart failure.[167,168] These benefits are likely to reflect an anti-ischemic action of ACE inhibition, particularly given the

Groups	Events (%) Treatment (45,002)	Control (45,054)	RR (CI)
Previous disease:			
Post-MI	1681 (11.7%)	2207 (15.4%)	0.78 (0.74–0.84)
Other CHD	568 (8.7%)	744 (11.4%)	0.77 (0.68–0.87)
None	1088 (4.5%)	1469 (6.1%)	0.72 (0.66–0.80)
Age (years):			
≤65	1671 (6.1%)	2344 (8.5%)	0.74 (0.69–0.79)
>65	1666 (9.5%)	2076 (11.9%)	0.81 (0.76–0.88)
Sex:			
Male	2686 (7.8%)	3630 (10.6%)	0.76 (0.72–0.80)
Female	651 (6.1%)	790 (7.3%)	0.82 (0.73–0.93)
Treated hypertension:			
Yes	2038 (8.2%)	2596 (10.4%)	0.79 (0.74–0.84)
No	1299 (6.4%)	1824 (9.1%)	0.75 (0.70–0.81)
History of diabetes:			
Yes	776 (8.3%)	979 (10.5%)	0.78 (0.69–0.87)
No	2561 (7.2%)	3441 (9.6%)	0.77 (0.73–0.81)
Diastolic blood pressure (mm Hg):			
≤90	2711 (7.8%)	3590 (10.3%)	0.77 (0.73–0.81)
>90	618 (6.1%)	827 (8.2%)	0.76 (0.68–0.85)
Total cholesterol (mmol/L):			
≤5.2	748 (6.9%)	940 (8.6%)	0.76 (0.66–0.88)
>5.2–6.5	1678 (7.0%)	2246 (9.4%)	0.76 (0.71–0.82)
>6.5	896 (8.8%)	1220 (12.1%)	0.78 (0.72–0.84)
LDL cholesterol (mmol/L):			
≤3.5	1130 (6.8%)	1443 (8.7%)	0.76 (0.68–0.84)
>3.5–4.5	1374 (7.3%)	1814 (9.6%)	0.77 (0.71–0.83)
>4.5	801 (9.3%)	1120 (12.9%)	0.78 (0.72–0.85)
HDL cholesterol (mmol/L):			
≤0.9	1167 (9.3%)	1538 (12.1%)	0.76 (0.70–0.84)
>0.9–1.1	939 (7.4%)	1270 (10.2%)	0.76 (0.70–0.83)
>1.1	1207 (6.2%)	1595 (8.1%)	0.77 (0.71–0.84)
Triglycerides (mmol/L):			
≤1.4	1162 (7.3%)	1521 (9.6%)	0.78 (0.71–0.85)
>1.4–2.0	937 (7.1%)	1304 (9.8%)	0.77 (0.71–0.84)
>2.0	1217 (7.9%)	1564 (10.2%)	0.76 (0.69–0.83)
Overall	**3337 (7.4%)**	**4420 (9.8%)**	**0.77 (0.74–0.80)**



Global test for heterogeneity: χ^2_{15}–15.1; p=0.4

Treatment effect P <0.0001

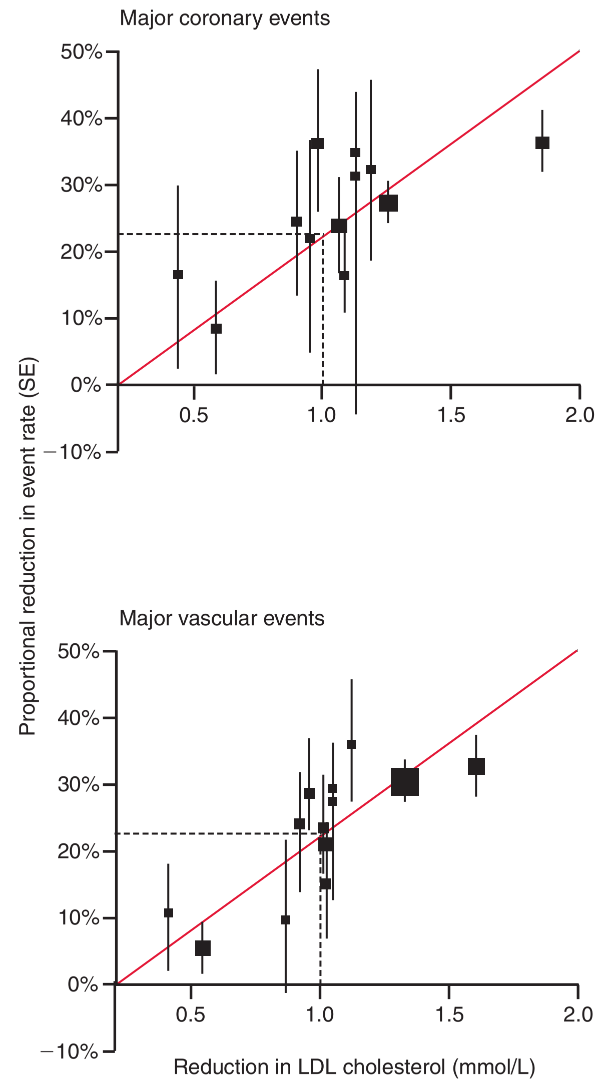


Figure 12–15 Benefits of statin therapy in subgroups of at-risk populations (*left panel*) are proportional to reductions in low-density lipoprotein cholesterol concentrations (*right panel*). Cholesterol concentration conversion; 1 mmol/L = 38 mg/dL. (Reproduced with permission from the Cholesterol Treatment Trialists' Collaboration [Lancet 2005;366:1267]).

evidence from the Heart Outcomes Prevention Evaluation [HOPE][169] and the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease [EUROPA] studies.[170] The HOPE study[169] was a large-scale randomized controlled trial of 9297 high-risk patients with vascular disease (55% with chronic stable angina) in the absence of documented heart failure. During the 4.5 years of follow-up, ramipril was associated with reductions in all-cause mortality, MI, and stroke.[169] These beneficial effects appeared to be independent of the associated reductions in blood pressure and were particularly marked in patients with diabetes mellitus.[171] These findings have been subsequently confirmed in the EUROPA trial of 13,655 patients with stable coronary heart disease.[170] Perindopril 8 mg daily was associated with a 20% relative risk reduction in the likelihood of cardiovascular death, myocardial infarction, or cardiac arrest: 50 patients needed to be treated for 4 years to avoid one event. The Prevention of Events with Angiotensin Converting Enzyme inhibition [PEACE] trial[172] contrasts to the HOPE[169] and EUROPA[170] trials because it failed to demonstrate a benefit of trandolapril in 8,290 patients with stable coronary heart disease. However, the event rate in this trial was unexpectedly low and was below the rate in the treatment arms of both the HOPE and EUROPA trials.[169,170]

All patients with chronic stable angina with a predicted 10-year event rate >15% should be maintained on chronic ACE inhibitor therapy because of the associated major secondary preventive benefits.

Coronary Revascularization

There have been no randomized controlled trials to demonstrate that PCI improves long-term prognosis and survival in patients with chronic stable angina. Indeed, several studies indicated that PCI is associated with a worse medium-term prognosis than medical therapy.[100,154] In contrast, in selected groups, CABG is associated with significant reductions in mortality rates compared with medical therapy. Comparisons of the prognostic benefits of PCI and CABG demonstrated no statistically significant differences between the two approaches,[102,103] but this does not establish equivalence. In the context of chronic stable angina, PCI remains an important treatment to relieve symptoms but is associated with a small early risk.

Coronary Artery Bypass Graft Surgery

In comparison with medical therapy, CABG improves long-term (10-year) survival in patients with stable angina. Subgroup analysis demonstrates that patients with greater than 50% left main stem stenosis had the greatest survival benefit with CABG.[12,138,173] Survival benefits are also seen in patients with three-vessel disease or two-vessel disease that includes proximal LAD stenosis.[12,138] However, patients with two-vessel disease without proximal LAD stenosis or one-vessel disease do not derive any survival advantage from CABG. Patients with abnormal left ventricular function or strongly positive exercise tests derive greater absolute survival benefit from CABG than from medical therapy.

The survival benefit for coronary artery surgery is, therefore, related to the severity of coronary artery disease. Those with the most severe coronary artery disease have the most to gain from coronary artery surgery, and the benefits are greatest in those with left main stem disease, followed by those with three-vessel disease and then by those with one- or two-vessel disease (see Figs. 12–10 and 12–13). Further observational evidence from the Duke University data base supports the observation that patients with two-vessel disease that involves the proximal LAD and those with three-vessel disease have a lower hazard ratio (for mortality) with CABG than do those who receive medical treatment.[106]

It is important to note that in the trials cited earlier, a significant number of patients with three-vessel disease who were initially randomized to medical therapy crossed over to surgery (41% at 10 years). These studies are, therefore, not a sole comparison of surgery and medical therapy but rather a comparison of initial surgical versus initial medical treatment. This factor has diluted the observed benefits of CABG because a high proportion of the patients initially randomized to medical therapy may have gained a survival benefit from surgery. In the meta-analysis of Yusuf and colleagues,[138] only 9.9% of patients received an internal mammary artery graft and only 25% of the patients who underwent CABG were receiving antiplatelet agents. These randomized controlled trials may have underestimated the benefits of CABG and do not take into account improvements in surgical techniques (see Fig. 12–10).[174]

POTENTIAL FUTURE THERAPIES

Angiogenesis

Angiogenesis is a novel area of interest that has therapeutic potential in patients considered unsuitable for conventional means of coronary revascularization. Growth factors that can induce new vessel growth—such as vascular endothelial growth factor (VEGF) or basic fibroblast growth factor—are administered into areas of ischemic myocardium, either as the mature peptide[175] or via gene transfer therapy,[176,177] to enhance collateral blood vessel formation and thereby improve myocardial blood flow and perfusion.

Early studies in lower-limb circulation[178] have suggested that there may be major clinical benefits from such an approach in patients with peripheral vascular disease and critical ischemia. Although there are concerns with regard to the potential for sarcomatous transformation, preliminary pilot studies within the coronary vascular bed have suggested that the implantation of microspheres impregnated with basic fibroblast growth factor[175] or gene transfer of VEGF[176,177] into ischemic, viable, but not graftable territories of myocardium can result in a significant enhancement of myocardial perfusion without provoking adverse effects.

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SECTION 3

Heart Failure

Chapter 13

Risk Factor Management and Lifestyle Modification in Heart Failure

Gene A. Gulliver and Nancy K. Sweitzer

CHAPTER CONTENTS

Heart failure is the final common pathway of most other cardiac diseases, including coronary heart disease (CHD), valvular disease, congenital heart disease, and hypertensive heart disease. Heart failure affects 5 million people in the United States, and millions more are at risk for developing heart failure. The cost to Medicare for beneficiaries with heart failure is 431% that of other beneficiaries; heart failure costs an estimated 28 billion dollars each year in the United States.[1] Despite tremendous advances in treatment during the past 25 years, heart failure remains a largely incurable and eventually fatal disease. It is increasingly argued that prevention of heart failure will have a greater impact to reduce the societal and individual burdens of this disease than any advances in treatment of established heart failure, owing to the size of the population at risk.[2] Risk factor management and lifestyle modification in heart failure will arguably have the greatest impact when focused on patients with early stages of disease.

The 2001 ACC/AHA Guidelines for the Prevention and Treatment of Chronic Heart Failure in the Adult first introduced the concept of preclinical heart failure as stages A and B, reinforced in the 2005 revision.[3,4] The stage A patient has risk factors for heart failure without detectable cardiovascular abnormalities or disease. The stage B patient has asymptomatic left ventricular dysfunction. (Fig. 13–1) To impact the tremendous economic and social costs due to heart failure, it is essential to target aggressive risk factor management and lifestyle modification to these early-stage heart failure patients. Risk factor management and lifestyle modification are also of critical importance to prevent disease progression in later-stage heart failure patients. Because risk assessment for heart failure is not part of routine clinical practice, increasing awareness in the medical community of the importance of identification and treatment of the stage A heart failure patient remains a great challenge. Most patients at risk for heart failure, and many with the disease, are unaware of the disease, and may attribute symptoms of fatigue and exertional intolerance to "normal" aging.

HEART FAILURE RISK ASSESSMENT

Successful heart failure risk assessment and risk reduction involve several objectives. First, appropriate recognition of risk must be achieved. Historically, recognition of heart failure risk in the medical community has been suboptimal. Although routine assessment of risk factors for coronary heart disease has been widely incorporated into medical practice, heart failure is rarely identified or discussed as a risk with patients, particularly in the large number of hypertensive patients at risk. Consequently, the vast majority of patients at risk for heart failure are neither aware of the disease nor of their risk of developing heart failure. In fact, as many as 25% of patients diagnosed with heart failure are unaware of the diagnosis.[5] Although many potential risk factors have been identified for heart failure (Table 13–1), simple, rapid risk assessment schemes similar to the coronary heart disease (CHD) risk estimates based on the Framingham Heart Study have not been developed.[6] Much of heart failure risk is clustered in a few risk factors, particularly CHD, hypertension, and diabetes.

Following identification of risk factors for heart failure, appropriately aggressive treatment must be initiated. Appropriateness is determined to an extent by the age of the patient because risk of new heart failure is significantly increased in the elderly. In addition, clustering of risk factors and magnitude of risk are important to recognize. In patients with multiple risk factors, short-term risk is elevated, and individual risk factors should be treated more aggressively, as is routine in the prevention of CHD.

Finally, optimal risk management in heart failure requires continual reassessment of risk. A patient at low risk for heart

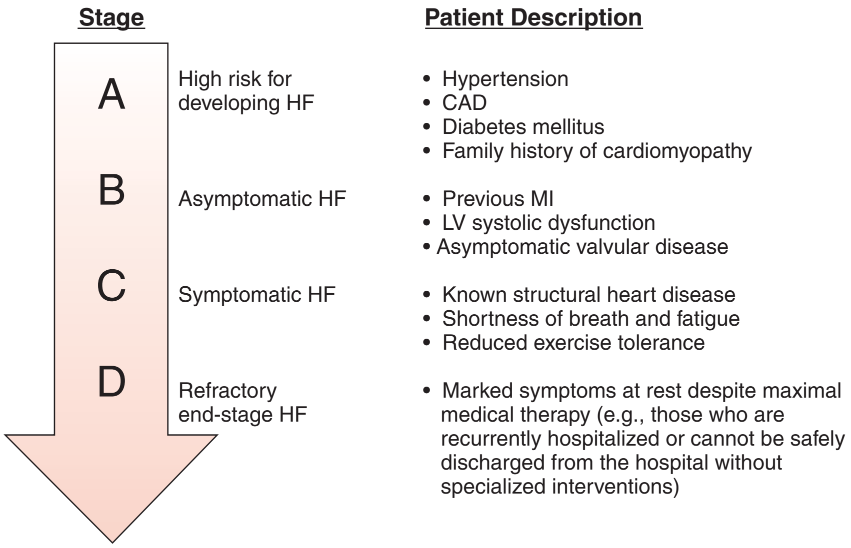

Figure 13–1 The ACC/AHA classification system for heart failure (heart failure).CAD, coronary artery disease; HF, heart failure; LV, left ventricular; MI, myocardial infarction.

Table 13–1 Identified Heart Failure Risk Factors

Coronary heart disease[7,10,13,28,29,34,35,73,170-172]	Male gender
Hypertension[7,10,13,55,60,61,86,173-180]	Alcohol[106,108,112]
Diabetes[65-67,73,74,79,181-183]	Atrial fibrillation[184,185]
Chronic kidney disease[73,82]	Elevated CRP/ESR[67,186,187]
Obesity[102,188-190]	Left ventricular hypertrophy (LVH)[10,191,192]
Metabolic syndrome[80]	Sleep apnea[115,118,195]
Physical inactivity[194]	Exposure to cardiac toxins
Microalbuminuria	Valvular heart disease[7,13]
Smoking[13,73,86]	Right ventricular pacing[195-197]
Depression[122,198,199]	

failure at age 45 may have significantly increased risk at age 55 after a myocardial infarction. Therefore, at each office visit, a component of the interaction should be dedicated to assessment and treatment of heart failure risk factors.

Risk Factors for Heart Failure

Many studies have explored risk factors for heart failure (see Table 13–1). Fewer studies have demonstrated the impact of treating risk factors on incidence of heart failure. Of the risk factors shown in Table 13–1, coronary heart disease (CHD), hypertension, and diabetes mellitus account for the majority of heart failure cases and carry the highest population-attributable risks (Fig. 13–2). Two large population cohort studies have provided invaluable data about heart failure risk: the Framingham Heart Study[7-12] and National Health and Nutrition Examination Survey 1 (NHANES).[13]

Risk for Heart Failure Secondary to Age, Gender, and Ethnic Background

Although not modifiable, demographic factors must be incorporated into risk assessment for heart failure. In the Framingham cohort, lifetime risk of developing heart failure is 21.0% for men and 20.3% for women aged 40 to 94 years old (Fig. 13–3).[7] Lifetime risk for heart failure does not change as age increases, which is unusual for chronic diseases. The result is a dramatically higher short-term risk for heart failure in elderly patients compared with younger patients. The extremely high short-term risk of heart failure in the elderly is under-recognized. Many diseases exhibit a decrease in lifetime risk during the elderly years as competing diseases of the elderly gain prominence. Heart failure incidence, in fact, is so increased in the elderly years, that competing comorbidities never overcome the risk of heart failure. As a result, aggressive risk factor assessment and management are warranted in the elderly, a traditionally undertreated group.[14,15]

Male gender is consistently associated with increased heart failure risk.[7,16] Heart failure risk is also elevated among African-Americans owing to the high prevalence of predisposing comorbidities, such as hypertension and diabetes.[13] African-Americans develop heart failure at an earlier age and present with more severe and advanced disease than do whites.[17-19] The underlying pathophysiology and response to treatment in African-Americans may also be different from those in white patients.[20,21]

Risk for Heart Failure Secondary to Coronary Heart Disease

It is clear that, in large part, assessing risk for heart failure is indistinguishable from CHD risk assessment. The majority of patients with systolic heart failure in developed countries have ischemic heart disease as the underlying etiology.[13,22] The

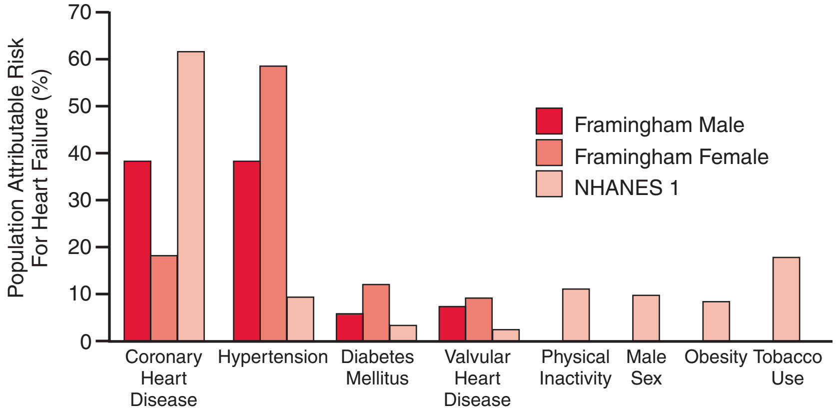

Figure 13–2 Population-attributable risk for heart failure for major heart failure risk factors—as determined by the Framingham Heart Study and the National Health and Nutrition Examination Survey 1 (NHANES).[13]

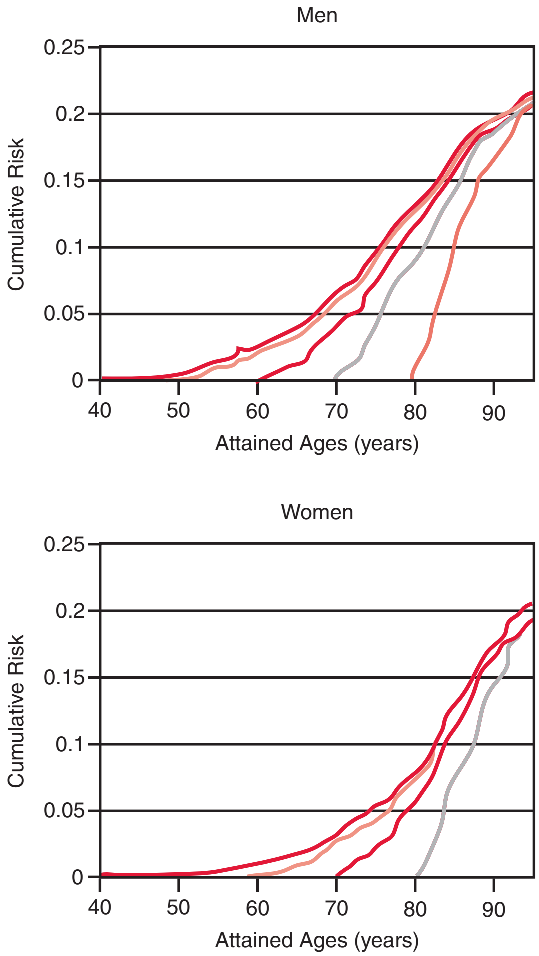

Figure 13–3 Cumulative risk for heart failure at selected index ages for men and women in the Framingham Heart Study. Lifetime risk for heart failure for given index age is cumulative risk through age 94 years. (Redrawn from Lloyd-Jones DM, Larson MG, Leip EP, et al: Lifetime risk for developing congestive heart failure: The Framingham Heart Study. Circulation 2002;106:3068-72.)

Framingham data demonstrate that men and women with angina have a 1.4 and 1.7 increase in relative risk for future heart failure, respectively, whereas after myocardial infarction, relative risk of future heart failure is markedly increased to 6.3 for men and 6.0 for women (see Fig. 13–2).[10] Because of a low prevalence of CHD in the Framingham cohort, the calculated population-attributable risk for heart failure due to ischemic heart disease is comparatively low, 34% for men and only 13% for women. In contrast, in NHANES there is a 62% population-attributable risk for heart failure due to CHD.[13] In the Cardiovascular Health Study, 44% of new heart failure was associated with a new CHD event.[23] It is clear that aggressive primary and secondary prevention of myocardial infarction will reduce the incidence of heart failure.

There are data evaluating the efficacy of treatment to reduce risk for heart failure in stages A and B heart failure patients with ischemic heart disease or disease equivalent. In stage B patients with a prior MI, asymptomatic left ventricular dysfunction, and no symptoms of heart failure, ACE inhibitors (ACEI) and β-blockers have been shown to delay onset of heart failure symptoms and reduce death.[24-27] The Heart Outcomes Prevention Evaluation (HOPE) trial enrolled patients with known vascular, disease or diabetes mellitus combined with multiple risk factors. Subjects were randomized to ramipril 10 mg or placebo.[28] A 20% reduction in future heart failure was noted in the ramipril-treated patients. Likewise, a post-hoc analysis of patients from the Scandinavian Simvastatin Survival Study (4S) trial examined CHD patients treated with simvastatin versus placebo, and found a 21% reduction in future risk of heart failure in patients treated with simvastatin.[29] Interestingly, in both the HOPE and 4S trials, approximately one half of the heart failure risk reduction was due to secondary prevention of myocardial infarction. The other one half of the risk reduction could not be explained by MI prevention, suggesting that these drugs may have effects to prevent heart failure in addition to their effects to prevent MI, perhaps related to neurohormonal, myocardial remodeling, or vascular effects.[30-33] The Treating to New Targets [TNT] trial tested the efficacy of intensive lipid-lowering therapy in 10,001 patients with CHD (stages A and B heart failure) and a mean LDL of <130 mg/dL. Subjects were randomized to atorvastatin 10 mg or 80 mg daily with a median follow-up of 4.9 years. There was a 25% reduction in hospitalization for heart failure in the higher dose atorvastatin group—suggesting that intensive lipid-lowering therapy prevents development of heart failure.[34] In the clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial more than 12,000 patients with acute coronary syndromes were randomized to clopidogrel or placebo.[35] There was a significant 18% reduction in incidence of in-hospital heart failure in the clopidogrel-treated group, suggesting that more

aggressive antiplatelet therapy may have effects to reduce heart failure risk, perhaps through increased myocardial salvage.

In the patient with established stages C and D heart failure due to ischemic heart disease, aggressive secondary prevention is, of course, warranted. β-Blockers and ACE inhibitors should be prescribed to all patients with systolic dysfunction. Some controversy exists about the use of aspirin in patients with heart failure owing to the potential detrimental effects of inhibition of prostaglandin synthesis by aspirin.[36-39] Several trials, however, suggest no impairment in ACE inhibitor efficacy in aspirin-treated patients, and it is routine to treat patients with ischemic heart failure with daily low-dose aspirin therapy.[40-44] Until data are available about the safety of aspirin in heart failure patients without CHD, it has been recommended that aspirin not be used for primary prevention in the patient with nonischemic cardiomyopathy, and the usefulness of aspirin in CHD patients without recent ischemic events has been questioned.[39] There is also some controversy over lipid-lowering therapy. Increasing data suggest that lipid-lowering therapy is of benefit in patients with heart failure, including those with nonischemic disease and diastolic dysfunction.[45-48] Some, however, have argued that aggressive lipid lowering may be harmful in subjects with advanced heart failure, based on the association between low lipid levels and increased mortality in advanced heart failure populations.[49-51] A final controversial area is that of antioxidant vitamin use in heart failure. Despite a reasonable scientific rationale, results in trials of antioxidant vitamins have been disappointing, and patients in the vitamin E (400 IU/day) arm of the HOPE trial showed an increased risk of heart failure and hospitalization for heart failure.[28,52,53]

Although the link between CHD and heart failure is clear, the impact made by aggressive primary and secondary prevention remains largely undefined. Although the data just mentioned begin to explore this issue, future incidence of heart failure has not been regularly monitored in trials of CHD prevention. Nevertheless, it remains inarguable that aggressive preventive therapies in the patient with known CHD are warranted and will likely reduce the future burden of heart failure if applied universally.

Risk for Heart Failure Secondary to Hypertension

Hypertension is an important contributor both to heart failure incidence and heart failure exacerbations. In the Framingham study, the presence of hypertension increased heart failure risk approximately twofold in men and threefold in women (see Fig. 13–2).[10] The prevalence of hypertension is high in the Framingham study, giving a population-attributable risk of 40% for men, and 60% for women. Although ischemic heart disease and hypertension contributed equally to development of heart failure in men in the Framingham study, hypertension was much more predictive of future heart failure development in women. In the NHANES population there is a substantially lower 10% population-attributable risk for heart failure due to hypertension (see Fig. 13–2).[13]

The various components of blood pressure have been studied to determine their contribution to future development of heart failure. Increases in systolic blood pressure and pulse pressure are associated linearly with risk of heart failure, without a threshold.[54,55] Interestingly, there appears to be a U-shaped association between diastolic BP and heart failure with increased risk at both the lowest and highest diastolic pressures.[55] This is likely due to the association between low diastolic blood pressure and increased arterial stiffness, with increased pulsatile load on the left ventricle contributing to heart failure development.

Numerous studies have demonstrated that treatment of hypertension reduces heart failure risk. Meta-analyses of trials of hypertension treatment with heart failure identified as an endpoint demonstrate a 22% to 80% reduction in risk of heart failure (select trials are shown in Table 13–2).[56,57] Agents shown to achieve reductions in incidence of heart failure include diuretics, ACE inhibitors, β-blockers, and probably angiotensin-receptor blockers.[58,59] Other antihypertensive medications, such as α-blockers and calcium channel blockers may increase heart failure risk. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), treatment of hypertension with doxazosin increased risk of future development of heart failure compared to chlorthalidone.[60] α-Adrenergic blocking drugs should not be used as an antihypertensive agent in patients at risk for heart failure. Similarly, the International Nifedipine GITS Study: Intervention as a Goal in Hypertensive Treatment (INSIGHT) trial found an increased risk of future heart failure in patients treated with nifedipine compared with those treated with the diuretic co-amilozide.[61] These data suggest that calcium channel blockers should not be used as first line agents in hypertensive patients at risk for heart failure, reinforcing the concept that the choice of antihypertensive medication, especially in patients at risk for heart failure, is of significant importance.

Heart failure is a complex endpoint in hypertension trials. Although diuretics have been associated with decreased inci-

Table 13–2 Incident Heart Failure in Select Hypertension Trials

	Number Enrolled	Age (years)	Heart Failure Risk Reduction (%)
EWPHE	840	>60	22
Coope and Warrender[176]	884	60-74	32
STOP-Hypertension	1627	70-84	51
SHEP	4736	60	47
STONE	1632	60-79	68

EWPHE: European Working Party on High blood pressure in the Elderly trial.[175]
STOP: hypertension—Swedish Trial in Old Patients with hypertension.[174,178]
SHEP: Systolic Hypertension in the Elderly Program.[173]
STONE: Shanghai Trial Of Nifedipine in the Elderly.[177]

dence of heart failure, it is not known if this might, in fact, be due to lower incidence of edema in diuretic-treated patients, and thus reduced diagnosis of heart failure. Conversely, lower extremity edema is a known side effect of calcium channel blockers; whether this leads to overdiagnosis of heart failure in this subgroup in clinical studies is unknown. The fact that there has been no uniform definition of heart failure in these studies further clouds the data. Nevertheless, it is clear from multiple studies that there is no substitute for effective treatment of hypertension. Until further data are available, the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure provides appropriate guidelines.[62]

Risk for Heart Failure Secondary to Diabetes Mellitus

Diabetes has been shown to be strongly associated with increased heart failure risk; however the interaction between diabetes and heart failure is complex, with diabetes being an etiology as well as a consequence of heart failure.[63,64] Poor glycemic control may be related to heart failure via multiple mechanisms—among them promotion of atherosclerosis and subsequent coronary heart disease; development of diabetic cardiomyopathy, possibly related to microangiopathy; and metabolic derangement reducing efficiency of myocardial performance.[65] In the Framingham study, the presence of diabetes mellitus doubles the risk of future heart failure development in men, and quadruples the risk in women.[11] Because of a relatively low prevalence of diabetes in this cohort, the population-attributable risk is 6% and 12% for men and women, respectively (see Fig. 13–2). In NHANES, the population-attributable risk of heart failure due to diabetes mellitus is 3.1%. With the rising incidence of type 2 diabetes mellitus, these population statistics will undoubtedly change, and diabetes will gain increasing prominence as a risk factor for heart failure.

The correlation between glycemic control and heart failure incidence has been explored in a large cohort of type 2 diabetic patients.[65] In this study, each 1% increase in hemoglobin A1C was associated with an 8% increase in risk of heart failure (Fig. 13–4). In a retrospective study evaluating incidence of heart failure in patients with impaired glucose tolerance, the incidence of heart failure increased as the level of fasting blood glucose (FBG) increased from <90 to 125.[66] Additionally, the Uppsala Longitudinal study of Adult Men demonstrated that degree of insulin resistance was associated with heart failure incidence independent of other risk factors.[67] These studies demonstrate a graded increase in heart failure risk from subclinical insulin resistance to impaired fasting glycemic control to diabetes mellitus. It has not been demonstrated that tighter glycemic control reduces heart failure risk in patients with diabetes.

When diabetes is clustered with other risk factors, risk of heart failure development is extremely high, and the need for aggressive treatment of all risk factors is even more compelling. The patient with diabetes appears to be more susceptible to ischemic injury of the myocardium. In studies comparing cardiac function in nondiabetic and diabetic patients after treatment with thrombolytics for acute myocardial infarction, patients with diabetes demonstrated impaired recruitment of contractile reserve in noninfarct segments,[68,69] greater reduction in global LV function,[70] and greater incidence of heart failure.[71,72]

The Type 2 Diabetes, Hypertension, Cardiovascular Events and Ramipril (DIABHYCAR) study defined risk factors for progression to heart failure among diabetic patients.[73] Age, history of CHD, urine protein, HgbA1C, and smoking >15 cigarettes a day independently predicted heart failure development in multivariate analysis (Table 13–3). In the OASIS

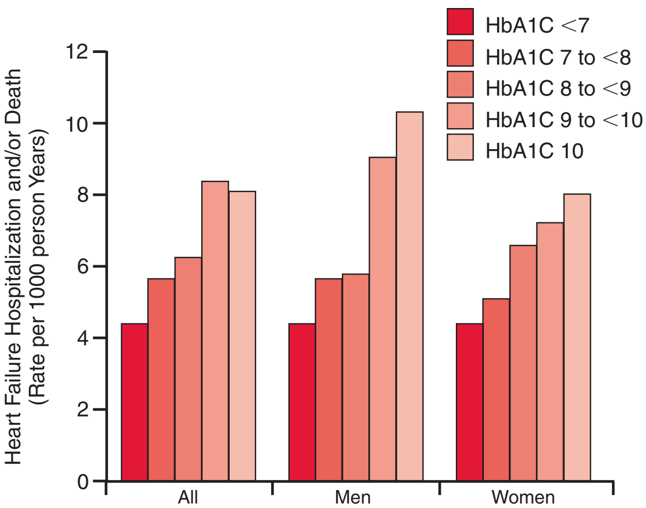

Figure 13–4 Rate of heart failure hospitalization and death in 48,858 persons stratified by hemoglobin A1C level (*P* value for trend = .0001). (Adapted from Iribarren C, Karter AJ, Go AS, et al: Glycemic control and heart failure among adult patients with diabetes. Circulation 2001;103:2668-73.

Table 13–3 Predictors of Heart Failure in Diabetes Mellitus

	Hazard Ratio	95% Confidence Interval	*P* Value
Age (for every 10-year increase)	1.72	1.68-1.76	<0.0001
History of cardiovascular disease	2.55	1.80-3.62	<0.0001
Urine albumin/creatinine ratio (per 10-fold increase)	2.30	1.71-3.09	<0.0001
Hemoglobin A1C (for every 1% increase)	1.80	1.08-1.29	0.0003
Smoking >15 cigarettes/day	1.98	1.15-3.40	0.013

Adapted from Vaur L, Gueret P, Lievre M, et al: Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: Observations from the DIABHYCAR (type 2 diabetes, hypertension, cardiovascular events and ramipril) study. Diabetes Care 2003;26:855-60.

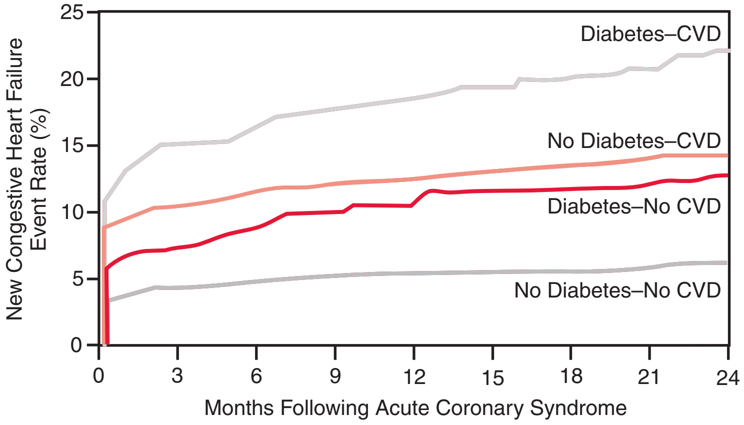

Figure 13–5 Risk of future heart failure in patients presenting with acute coronary syndromes, stratified by the presence or absence of known diabetes or cardiovascular disease (CVD) at the time of presentation. Data from the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry. (Redrawn from RW Nesto, Rev Cardiovasc Med 2004;5:1-8; adapted from Malmberg K, Yusuf S, Gerstein HC, et al: Impact of diabetes on long-term prognosis in patients with unstable angina and non–Q-wave myocardial infarction: Results of the OASIS [organization to assess strategies for ischemic syndromes] registry. Circulation 2000;102:1014-9.)

registry, patients were enrolled at the time of an acute myocardial infarction and future risk of heart failure was evaluated.[74] Those patients without a previous history of diabetes mellitus or known cardiovascular disease at the time of their acute presentation demonstrated an approximate 5% risk of heart failure over the next 2 years. If at presentation there was a history of diabetes mellitus, but no history of cardiovascular disease, or the inverse, then the risk of heart failure over the next 2 years approximately doubled. However, in patients with both a history of diabetes mellitus and known cardiovascular disease, an approximate 20% risk of new heart failure over the next 2 years was observed (Fig. 13–5).

Heart failure risk also has been examined in patients with combined hypertension and diabetes. The United Kingdom Prospective Diabetes Study Group (UKPDS) documented the importance of blood pressure control in those patients with diabetes mellitus to reduce heart failure.[75] In this study, 1200 subjects with type 2 diabetes were randomized to "tight" blood pressure control (treating to less than 150/85) or less strict blood pressure control (treating to less than 180/105). Over 8 years of follow-up, the authors reported a 50% reduction in development of heart failure in the tight blood pressure control group.

The Losartan Intervention for Endpoint Reduction (LIFE) trial provides yet more detail with regard to the importance of specific therapies for treatment of hypertension in the setting of diabetes mellitus.[58] Of 9193 patients randomized to treatment with losartan 50 mg or atenolol 50 mg, a subgroup of 1195 subjects had both hypertension and diabetes. Although overall the incidence of heart failure was not different between individuals receiving the two therapies at 5 years of follow-up, the diabetic subjects had significantly fewer hospitalizations for heart failure when treated with losartan (5% versus 9%; $P = 0.019$), emphasizing the importance of angiotensin system blockade as a therapeutic maneuver in subjects with diabetes mellitus. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial investigated effects of the two β-blockers on glycemic and metabolic control in patients with diabetes and hypertension.[76] Carvedilol was associated with improvement in components of the metabolic syndrome and no disturbance in glycemic control. Incidence of clinically important endpoints, such as heart failure, was not reported in this short-duration study.

Investigators have attempted to determine possible pathophysiologic mechanisms for the detrimental synergy between diabetes and hypertension.[77] Interestingly, although diabetic hearts demonstrate hypertrophy, cavity dilation, and depressed ventricular performance, these alterations are more severe in patients with combined diabetes and hypertension. In addition, the risk of heart failure in diabetics has been reported to be out of proportion to the degree of ventricular remodeling seen,[78] suggesting that diastolic abnormalities are important in the diabetic population. Studies have also demonstrated apoptosis and necrosis in ventricular myocardial biopsies obtained from both diabetic-hypertensive patients and diabetic patients, with similar levels of apoptosis in both the diabetic and diabetic-hypertensive patients, but increased levels of cellular necrosis in patients with both diabetes and hypertension.[77] An associated increase in angiotensin II labeling in myocytes and endothelial cells was more significant in patients with diabetes and hypertension, than in patients with diabetes alone.

The aforementioned findings provide a possible pathophysiologic basis for the importance of blockade of the renin-angiotensin-aldosterone system in patients with both diabetes and hypertension. The importance of blockade of this system has also been demonstrated when diabetes is combined with renal disease. In the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) trial, diabetic patients with overt nephropathy were randomized to either losartan (50 to 100 mg once a day) or placebo.[79] The incidence of first hospitalization for heart failure was reduced by 30% in the group treated with losartan—further emphasizing the importance of RAAS blockade.

Risk for Heart Failure Secondary to Metabolic Syndrome

The relation between metabolic syndrome and heart failure is also being explored. The Adult Treatment Program III of the National Cholesterol Education Program has defined the metabolic syndrome as the presence of three or more of the following: (1) hypertension; (2) impaired fasting glucose; (3) low HDL cholesterol; (4) increased triglycerides; (5) and abdominal obesity. In one case control study, patients with metabolic syndrome and an acute myocardial infarction had an increased incidence of severe in-hospital heart failure.[80] Of the five metabolic syndrome components, hyperglycemia was the major determinant of severe heart failure. In the Women's Ischemia Syndrome Evaluation study, 25% of women referred for coronary angiography met criteria for the metabolic

syndrome. In subjects with angiographically significant CHD, the metabolic syndrome was associated with higher rates of major adverse cardiovascular events including stroke and heart failure.[81]

Risk for Heart Failure Secondary to Renal Disease

Renal disease, especially microalbuminuria, is strongly associated with increased incidence of first hospitalization for heart failure.[82] The mechanism by which renal disease causes heart failure is unknown, although vascular stiffening, uremic toxins, and impaired fluid balance have been implicated.[83-85] Microalbuminuria may be a marker of poor glycemic control, hypertension, inflammation, and/or endothelial dysfunction. In the DIABHYCAR study, a 10-fold increase in urinary albumin concentration more than doubled the risk of heart failure.[73] It is unknown whether treatment of renal disease, including microalbuminuria, will independently reduce the risk of future heart failure. The risk for heart failure secondary to renal dysfunction was evaluated by analyzing data obtained from the Heart Outcomes Prevention Evaluation (HOPE) trial.[82] Patients were stratified by the presence or absence of microalbuminuria. The risk of heart failure was higher in the group of patients with microalbuminuria, indicating that the presence of renal disease is a marker of risk for heart failure. However, treatment with ramipril did not reduce risk of future heart failure in the microalbuminuric subjects, suggesting that ACE inhibitor therapy was not particularly effective at heart failure prevention in this group of patients with renal dysfunction and microalbuminuria.

Risk for Heart Failure Secondary to Tobacco Use

Smoking cessation is an important component of primary and secondary prevention of both coronary artery disease and heart failure. In one study, after adjusting for hypertension, body weight, and other heart failure risk factors, patients actively smoking at the age of 50 demonstrated a 60% higher risk of future heart failure.[86] Likewise, after adjustment for other risk factors, active smokers in NHANES demonstrated a 45% (men) and 88% (women) increase in the risk of heart failure.[13] In fact, in NHANES, 17% of the population-attributable risk for heart failure was due to cigarette smoking. Independent of tobacco use promoting physiologic abnormalities that increase the risk of coronary artery disease, it has been hypothesized that cigarette smoking induces oxidative stress, which may promote LV remodeling[87] and have direct toxic effects on the myocardium.[88,89] All patients, whether healthy, at risk for heart failure, or with known cardiovascular disease and heart failure, should be counseled to quit smoking as recommended in the ACC/AHA guideline.[4] In addition, cardiologists should be comfortable in prescribing effective treatment to assist with smoking cessation, rather than relying on primary care physicians for this critical intervention.

Risk for Heart Failure Secondary to Valvular Abnormalities

An increased risk for heart failure has been noted in patients with valvular abnormalities, determined both by clinically significant precordial murmurs,[6,9] or diagnostic codes recorded in the medical record.[13,90] Valvular heart disease results in either pressure or volume overload of the ventricle. The left ventricle initially tolerates the overload via compensatory mechanisms such as hypertrophy or dilatation. Over time, however, as in other cardiovascular disorders, chronic hemodynamic overload results in left ventricular dysfunction and eventually overt heart failure.[91] Significant improvement in left ventricular function and survival has been achieved with surgical management of stenotic and regurgitant diseases of the aortic and mitral valves.[91,92] Survival can be improved with acceptable operative mortality even in the elderly, and there is no reason to delay valve surgery in appropriate patients once heart failure symptoms are present.[93,94]

Risk for Heart Failure Secondary to Obesity

The relation between obesity and heart failure risk is complex because obesity invariably clusters with other risk factors. Nevertheless, a number of studies indicate that obesity is a potent predictor of subsequent development of heart failure. Data collected on 5881 participants from the Framingham Heart Study during a mean follow-up of 14 years showed a significant increase in risk of heart failure with increased body mass index (BMI) (Fig. 13–6).[12] In this analysis, heart failure developed in 496 subjects—258 women and 238 men. After adjusting for numerous risk factors, the investigators noted that for each 1 unit increase in body mass index, there was an increased risk of heart failure of 5% for men, and 7% for women. Compared with subjects with normal body mass index, the hazard ratios for development of heart failure in obese men and women were 2.12 (95 % CI: 1.51 to 2.97) and 1.90 (95%CI: 1.30 to 2.79), respectively. These data suggest that incidence of heart failure rises steeply as body weight increases.

Although it has not been definitively demonstrated that weight loss reduces heart failure risk, several studies suggest that weight loss may be an important intervention for regression of left ventricular hypertrophy and prevention of heart failure in obesity. Case reports of extreme weight loss induced by biliopancreatic diversion have reported recovery from severe heart failure with associated near normalization of cardiac structure and function.[95-97] Alpert and colleagues performed echocardiograms on obese patients before and following bariatric surgery and found that weight loss was associated with reductions in left ventricular chamber size, wall stress and mass, and an improvement in diastolic function.[97] In an observational study of patients undergoing gastroplasty compared with controls treated with diet alone, weight loss following surgery correlated with LVH regression independent of reduction in blood pressure.[98] Conventional weight reduction through intensive diet and exercise has also been shown to reduce left ventricular mass.[99] Although LVH regression is associated with improved outcomes in hypertensive patients,[100] there are no data demonstrating reduced cardiovascular events with sustained weight loss in obese patients with LVH.

There are additional data demonstrating that the relation between obesity and heart failure is more complicated. It has been demonstrated repeatedly that obese patients with

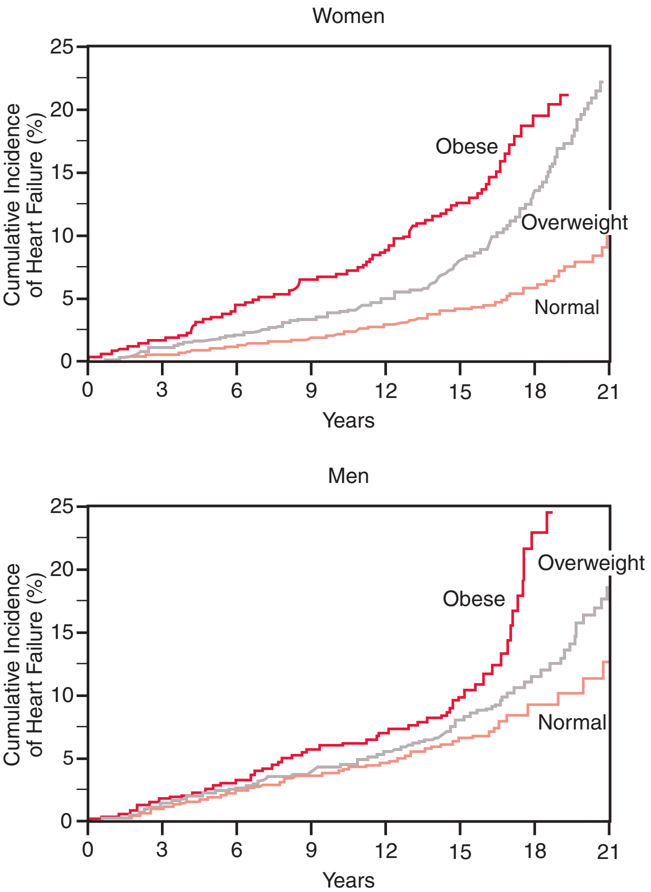

Figure 13–6 Cumulative incidence of heart failure from the Framingham Heart Study, stratified by body-mass index at the baseline examination. The body-mass index was 18.5 to 24.9 in normal subjects, 25.0 to 29.9 in overweight subjects, and 30.0 or more in obese subjects. (Redrawn from Kenchaiah S, Evans JC, Levy D, et al: Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.)

diagnosed heart failure have a more favorable prognosis than heart failure patients with low, or even normal BMI—the "obesity paradox."[101,102] The term "reverse epidemiology" has been used to describe the phenomenon wherein conventional cardiovascular risk factors, in addition to obesity, are associated with better prognosis in chronic heart failure.[50] Possible explanations of the "obesity paradox" include (1) increased risk in patients with low body weight as a result of a high catabolic state due to the presence of more severe disease with higher levels of proinflammatory cytokines[103]; (2) relatively less neurohormonal activation or greater metabolic reserve in obese patients[104]; and (3) lead-time bias—in that obesity leads to development of symptoms and subsequent diagnosis when at a less advanced stage of disease.[105]

Risk of Heart Failure Secondary to Alcohol Consumption

The relation between excessive alcohol consumption and cardiomyopathy, the result of toxic injury to the cells of the myocardium, is well accepted.[106,107] In a Swedish cohort of men, history of alcohol abuse was associated with an increased risk of heart failure.[108] A history of heavy alcohol use has been shown to be correlated with systolic dysfunction,[109-111] whereas mild-to-moderate alcohol consumption has been inversely associated with risk of heart failure[112,113] and after a myocardial infarction, there is a reduced risk of new heart failure in light-to-moderate drinkers (one to ten drinks per week).[114] This effect of mild-to-moderate alcohol consumption to reduce heart failure is possibly mediated by decreasing the risk of CHD and subsequent MI. Patients at risk for heart failure should be counseled to engage in no more than moderate drinking, although abstinence may be appropriate in patients with a history of alcohol abuse.

Risk for Heart Failure Secondary to Sleep-Disordered Breathing

Sleep-disordered breathing (SDB) includes the variants obstructive sleep apnea (OSA) and central sleep apnea (CSA). Among patients with heart failure, sleep-disordered breathing is common, with increased incidence of both OSA and CSA. Approximately one third of patients with heart failure and SDB have CSA.[115] Patients with CSA and heart failure have an increased mortality independent of other known risk factors.[116]

The pathophysiologic link between heart failure and SDB has been explored in a canine model.[117] Inspiration against an occluded airway can lead to an increase in left ventricular afterload, a decrease in preload, and a reduction in stroke volume. The reduced stroke volume may then lead to neurohormonal activation implicated in the primary pathophysiology of heart failure. Additionally, OSA may cause intermittent hypoxia and increased sympathetic tone, provoking myocardial ischemia and further increases in afterload. In a study of over 6400 individuals, the presence of an apnea-hypopnea index >11 per hour was associated with greater than 2.4-fold odds of self-reported heart failure.[118] Whether the sleep apnea contributed to heart failure development is unknown, and although there is a plausible pathophysiologic link, it remains unknown whether SDB can actually cause heart failure.

It has been shown that treatment of diagnosed SDB can result in some improvements in cardiac function. Treatment of CSA with CPAP in heart failure patients in one study improved left ventricular ejection fraction, and, possibly, mortality.[119] In another study, patients with dilated cardiomyopathy and OSA were treated with CPAP and had objective improvements in left ventricular end systolic volume and ejection fraction.[120] The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial enrolled 258 patients and demonstrated that patients treated with CPAP had a small improvement in ejection fraction without any effect on mortality.[121]

Risk for Heart Failure Secondary to Depression

The relation between the mind and physical diseases of the body has gained increasing attention. Recent studies have examined depression as a risk factor for heart failure. In the SHEP trial, enrolled subjects were elderly hypertensives who completed a questionnaire at the start of the trial assessing

depression. Over the next 5 years, patients with high depression scores had a higher risk of new heart failure.[122] A similar increase in risk has been found in depressed elderly women without other risk factors for heart failure although no increased risk was seen in men with depression.[123] Among patients with established heart failure, a coincident diagnosis of depression is associated with a worse prognosis.[124,125] These data raise the interesting possibility that treating depression might reduce an individual's risk for heart failure or reduce heart failure morbidity, but this has not been tested.

LIFESTYLE MODIFICATION IN THE HEART FAILURE PATIENT

The majority of Americans are sedentary.[126] Simultaneously, the availability of inexpensive high calorie and processed foods has led to an increase in fat, salt, and caloric intake—correlated with decreased leisure activity.[127] Tobacco use, while declining among adults, has been increasing in adolescents in recent years.[128] Thus, all persons must be aware of the health effects of lifestyle choices, and encouraged to change unhealthful behaviors. There are a number of lifestyle issues of specific importance to the patient with, or at risk for, heart failure.

Heart Failure and Diet

Dietary choices affect heart failure risk in many important ways,[129] including the risk of heart disease associated with a diet high in refined grain products and deficient in fish or fruit and vegetables, the contribution of salt to hypertension in a subset of individuals, and the general contribution of excess calorie intake to obesity, diabetes, and hypertension. It has been demonstrated that diet can influence risk of CHD,[130-132] which would then impact subsequent heart failure risk. Likewise, diet and weight reduction are clearly associated with both reductions in blood pressure[133] and improved glycemic control,[134] both of which would be expected to reduce heart failure risk.

Dietary interventions specifically applied to patients with heart failure include restriction of both sodium intake and fluid intake. Although there are no data to suggest that these dietary interventions reduce heart failure mortality, there is increasing evidence that sodium and fluid restriction improve quality of life. Heart failure patients randomized to sodium and fluid restriction have less edema and fatigue than those eating their usual diet.[135] The patients with sodium and fluid restrictions also had an improvement in physical activity and functional class, whereas levels of physical activity worsened in patients following their usual diet. Noncompliance with diet recommendations among heart failure patients is associated with readmission and longer lengths of stay.[136] There is no evidence that routine use of nutritional supplements can prevent cardiac dysfunction or injury,[137] nor have nutritional supplements or neutraceuticals been shown to have benefit to improve symptoms or outcomes in established heart failure. Excellent patient-oriented educational materials are available in print and on the Web, to assist patients with understanding of dietary recommendations and to provide aids for compliance (see e.g., *www.abouthf.org*).

Heart Failure and Alcohol Consumption

As noted earlier, the precise relation between alcohol consumption and heart failure is unknown. Acute and long-term effects of alcohol in patients with heart failure have recently been reviewed.[138,139] The authors concluded that at least some emerging evidence suggests that light drinking (1 to 14 drinks per week) is safe and even beneficial in heart failure patients with ischemic left ventricular dysfunction, but without benefit in patients with nonischemic left ventricular dysfunction. Men may derive more of the protective benefit of moderate alcohol consumption than women.[13,112] Given the known detrimental effects of alcohol on myocardial function, alcohol should be avoided during periods of clinical instability. Because cardiomyopathy due to alcohol ingestion can recover with abstinence or reduction in alcohol intake to moderate levels,[140] a period of abstinence is advisable in most patients presenting with new heart failure and systolic dysfunction, as alcohol use is often under-reported. Once cardiac function has stabilized, it may be reasonable to permit occasional alcohol use. However, because of the known toxic effects of alcohol on the myocardium, recommendations about alcohol should be made cautiously and tailored to the individual patient.

Heart Failure and Exercise

Skeletal muscle structure and function are abnormal in individuals with heart failure, which contributes to deconditioning and exercise intolerance.[141,142] Heart failure patients also exhibit attenuated peripheral vascular responses to exercise and reduced respiratory muscle endurance.[143,144] Regular exercise improves symptoms, clinical status, and exercise duration in patients with heart failure,[145] perhaps as a result of reversing peripheral abnormalities.[146] In one study, patients with stable heart failure were randomly assigned to exercise training or no exercise for 1 year. Exercise training improved functional capacity, quality of life, and reduced hospital admissions for heart failure.[147] In addition, there was a statistically significant reduction in mortality in the exercise-training group. Exercise also appears to have beneficial effects on ventricular structure and remodeling.[148]

The current NIH-sponsored trial Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) is designed to investigate the potential benefits of exercise on morbidity and mortality in heart failure patients in great detail. Until those results are available, exercise training should be recommended for all stable outpatients with chronic heart failure able to participate. A typical training regimen begins with very low-level, low-impact exercise such as walking 5 to 10 minutes per day, and increases gradually to 30 or more minutes at a moderate perceived level of exertion at least 5 days a week. Many outpatient cardiac rehabilitation programs have moved beyond caring exclusively for patients with coronary disease and have become experienced and comfortable providing exercise prescriptions and lifestyle advice to heart failure patients.

Heart Failure and Sexual Activity

The maintenance of sexual function has been shown to be a concern among patients with cardiac illness.[149,150] Satisfaction

with sexual relations in patients with heart disease can be affected by medications, exercise capacity, changes in mood and self-esteem, and fear of death by the patient and/or partner. The issue of sexual function has been studied in patients with advanced heart failure.[149] One half of patients reported significant reductions in their sexual satisfaction after the development of heart failure. There were correlations between both 6-minute walk performance and NYHA class, and level of sexual function. There was no significant relation between sexual function and ejection fraction. Sexual activity carries different risks depending on the severity of heart failure.[63] Although NYHA class I patients have minimal risk with sexual activity, risk increases as NYHA class increases. Unstable patients should be advised to abstain from sexual activity until the disease state has stabilized.

Treatment of sexual dysfunction in male subjects with sildenafil citrate has become commonplace. Sildenafil citrate can be used safely in men with erectile dysfunction and mild-to-moderate chronic heart failure, with flexible dosing of sildenafil well tolerated, improving erectile dysfunction, and increasing satisfaction with sexual performance compared with placebo.[151] Indeed, sildenafil may have a role in treatment of advanced heart failure with secondary pulmonary hypertension.[152,153] Patients receiving oral nitrate therapy should

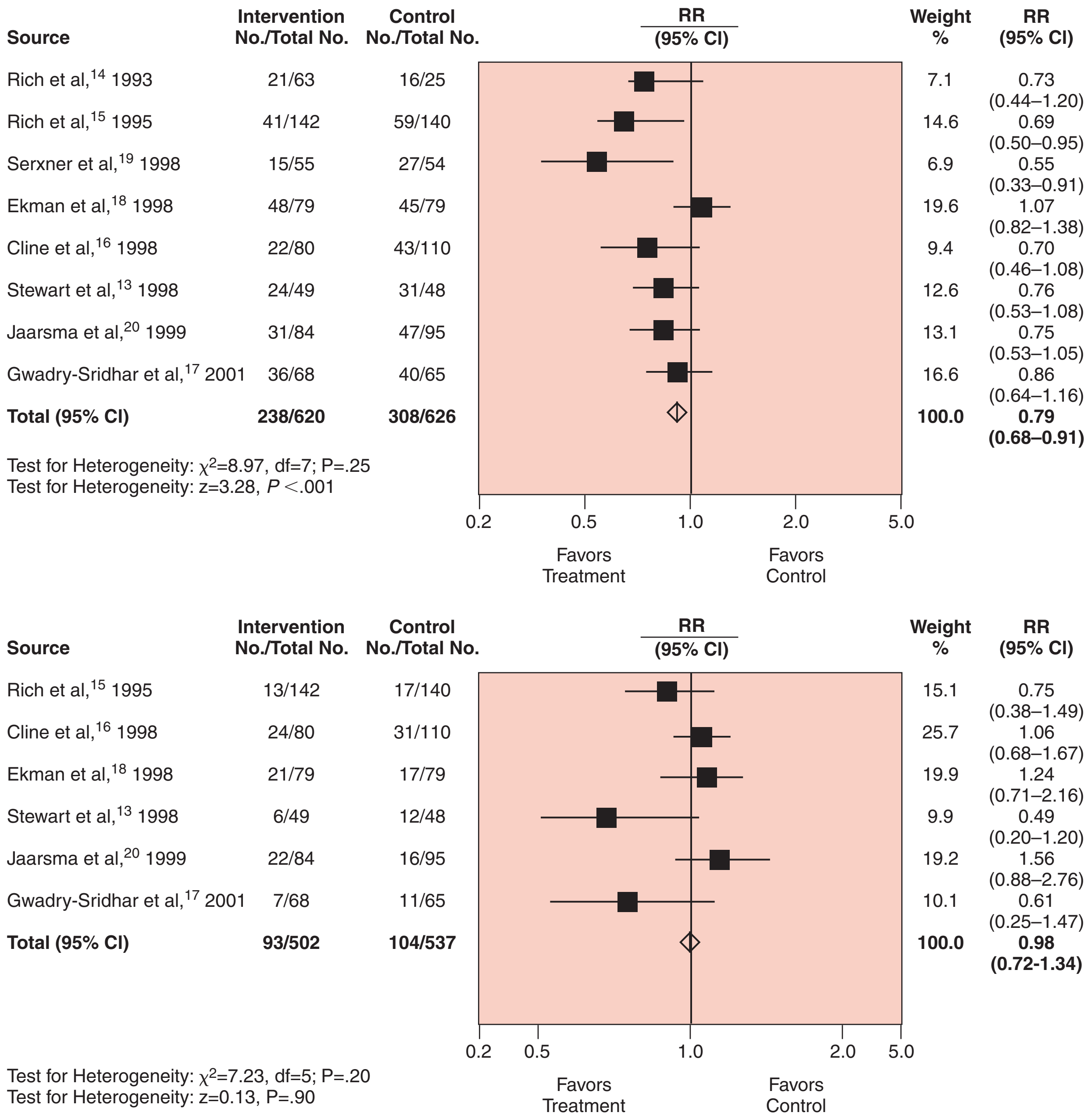

Figure 13–7 Data from a 2004 meta-analysis of heart failure disease management demonstrating a significant reduction in relative risk of heart failure readmission in the pooled analysis, with no effect on relative risk of mortality. RR, relative risk; CI, confidence interval. (Redrawn Gwadry-Sridhar FH, Flintoft V, Lee DS, et al: A systematic review and meta-analysis of studies comparing readmission rates and mortality rates in patients with heart failure. Arch Intern Med 2004;164:2315-20.)

not be prescribed sildenafil because of the risk of significant hypotension.

Heart Failure and Stress

There are no data demonstrating a causal link between mental stress and heart failure. However, as increased circulating catecholamines are implicated in the pathogenesis of heart failure, mental stress may contribute to disease progression through an increase in adrenergic stimulation.[154,155] There is increasing interest in exploring the mind-body relation and its impact in heart failure. The potential link between depression and heart failure is discussed earlier. Meditative and relaxation techniques have been shown to have benefits in patients with heart failure.[156-159] Acupuncture has been shown to decrease sympathetic activation in heart failure patients during periods of mental stress.[160] A randomized controlled trial of mind-body therapy showed improved exercise capacity and quality of life in patients participating in an unblinded Tai Chi program; it is unclear if it was the exercise component, the relaxation component, or the combination that conferred benefit.[161] In select patients, therapies directed at relaxation and stress reduction may hold promise for improvements of quality of life and functional capacity.

Managing Lifestyle Changes: The Role of Comprehensive Heart Failure Management Programs

Disease management has been shown to improve outcomes in heart failure and includes a significant educational component and assistance with lifestyle and risk-factor modification. Disease management programs use a comprehensive approach in patients with heart failure, identifying barriers to optimal disease and symptom control and using team resources to assist patients in their search for improved longevity and well-being.

Initial nonrandomized trials investigated the impact of optimization of drug therapy, intensive patient education, and vigilant follow-up, with particular attention paid to early recognition of decompensation, and identification and aggressive management of significant comorbidities and risk factors. This comprehensive approach resulted in significantly fewer rehospitalizations, lower health care costs, and improved functional and symptom status when compared with rates before referral to the disease management program, or to heart failure patients being treated with conventional care.[162-164] The first randomized clinical trial was a single-center study of high-risk heart failure patients. The authors evaluated the impact of a comprehensive approach that used nurse-directed, multidisciplinary disease management interventions on nonadherence to diet or medications, inappropriate prescribing of medications, and failure to recognize heart failure exacerbations. The results demonstrated a reduction in heart failure readmissions by 56% in 90 days, all readmissions by 29%, and overall cost of care by $460 per patient.[165] Subsequent randomized-controlled trials have demonstrated improvements in mortality, heart failure hospitalizations, all-cause hospitalizations, and reduction or no change in health care costs.[166-168] A meta-analysis has demonstrated a uniform trend for disease management to reduce readmission, with variable effects on mortality (Fig. 13–7).[169] It has been suggested that attention to risk factor and lifestyle management is greater in disease management clinics than with conventional care—possibly because of the high degree of nurse involvement.

Conclusions

A large population is at risk for future development of heart failure. Substantial impact, both economically and socially, will result from maximizing risk reducing therapies in this population. Much of this risk reduction involves lifestyle changes recommended universally to optimize heart health, whereas others are tailored to the individual patient and the risk factors present. Risk for heart failure must be continually reassessed as patients age, and no office visit should pass without a discussion of lifestyle and encouragement to change unhealthful behaviors. Likewise, lifestyle modification can have substantial impact in the patient with established heart failure, particularly to reduce symptom burden and enhance quality of life. Although change is slow, health care providers do influence patients' lifestyle choices and must continually stress the importance of changing often entrenched unhealthful behavior patterns to optimize care of patients with heart failure.

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Chapter 14

Pharmacologic Management of Heart Failure in the Ambulatory Setting

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CHAPTER CONTENTS

Heart failure is a growing public health problem.[1] Over the past decade, there has been considerable advancement in our understanding of the basic pathophysiologic mechanisms that underlie the clinical syndrome of heart failure, the progressive nature of left ventricular remodeling, and associated high mortality rates.[2] Randomized, controlled trials have demonstrated that medications such as angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists reduce the rate of mortality and improve functional status. Nonetheless, the morbidity rate associated with heart failure remains high, and many patients are not optimally treated.[3] These observations stimulated the formulation of specific guidelines for the management of patients with chronic heart failure.[4] A major emphasis in the coming years will include a continued search for more effective therapies as well as a significant educational effort to assist health care providers in the increased use of existing therapies.

This chapter reviews current pharmacologic treatment strategies for ambulatory patients with chronic heart failure. In each section, the most pertinent information regarding pathophysiologic mechanisms is presented, as well as data from important clinical trials that provide the scientific rationale for the treatment recommendations. For areas in which there is strong agreement on medical management, evidence-based recommendations from the ACC/AHA revised guidelines are provided.[4] For areas in which there are few data on mechanisms and treatment, the consensus opinion among heart failure specialists and empiric recommendations are discussed. In addition, each section includes practical recommendations that can be used in everyday clinical practice. A more detailed discussion of the drugs used in the treatment of heart failure can be found in Chapter 23 in HD7ed. Recommendations regarding preventive strategies and risk factor and lifestyle modification are provided in Chapter 13.

PATHOPHYSIOLOGY AND STAGING SYSTEM: TARGETS OF THERAPY

The basic pathophysiology of heart failure, including short-term adaptive mechanisms, chronic myocardial remodeling and neurohormonal, paracrine, and autocrine adjustments is extensively discussed in Chapter 21 in HD7e, as well as in other reviews.[5-7] Three important pathophysiologic concepts have had a substantial impact on the overall treatment strategy. The first concept recognizes the systemic nature of the clinical syndrome of heart failure. Although the primary problem is related to an abnormality in the myocardium, many of the manifesting signs and symptoms are related to dysfunction of end organs—including the lungs, liver, and kidneys—as well as skeletal muscle. The fact that heart failure is a systemic process makes it unlikely that any single therapy will offer a complete treatment response. A second important concept involves the interaction between myocardial dysfunction, activation of neurohormonal systems, and disease progression (Fig. 14–1). This model emphasizes the fact that although heart failure is related to a primary abnormality in myocardial function (genetic or acquired), further impairments in myocardial function, as well as progressive hypertrophy, dilatation or both, can occur in the absence of additional direct injury to the heart. This model can also help to explain the absence of signs and symptoms of heart failure in some patients who have significant ventricular dysfunction, and provides the rationale for therapy with ACE inhibitors and β-blockers in patients with asymptomatic left ventricular dysfunction. Finally, this model emphasizes the observation that treatments that do not have an intrinsic action on the primary myocardial abnormality can still have substantial benefits in heart failure. Thus, ACE inhibitors reduce vasoconstrictor tone and angiotensin-mediated toxicity in the heart, vasculature, and kidneys, and are associated with marked

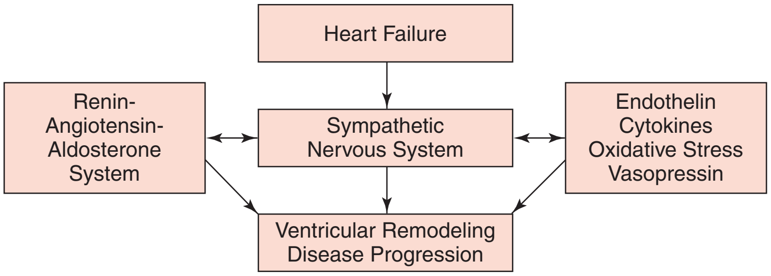

Figure 14–1 Proposed sequence of events in the progression of heart failure. After an initial injury, various secondary mediators such as norepinephrine, angiotensin, and mechanical stress act on the myocardium to cause ventricular remodeling. Additional biological mediators, including endothelin, proinflammatory cytokines, and reactive oxygen species, are upregulated in heart failure and contribute to disease progression.

Table 14–1 Drugs in Heart Failure: Divergent Effects on Therapeutic Goals

Drug	Mortality	Exercise Tolerance	Quality of Life
ACE inhibitor	↓ 20%	Mild improvement	Mild improvement
β-Blocker	↓ 35%	No or mild improvement	No or mild improvement
Aldosterone antagonist	↓ 30%	No or mild improvement	Mild improvement
Digoxin	No effect	Mild improvement	Unknown
Diuretic	Unknown	Moderate improvement	Moderate improvement

ACE, angiotensin-converting enzyme.

Table 14–2 Stage-Based Pharmacologic Therapy of Heart Failure

Stage	Drug	Selected Indications
A	ACE inhibitor or ARB	Vascular disease, diabetes, hypertension
B	ACE inhibitor or ARB	Recent or remote MI, asymptomatic LVD, hypertensive LVH
	β-Blocker	Recent or remote MI, asymptomatic LVD
C	ACE inhibitor or ARB	All patients unless contraindicated
	β-Blocker	All patients unless contraindicated
	Diuretics	Fluid retention
	Aldosterone antagonist	Severe heart failure, post-MI heart failure, or LVD
	Hydralazine and nitrates	Symptomatic heart failure, African Americans
	ARB (on top of ACE inhibitor)	Symptomatic heart failure
	Digoxin	Symptomatic heart failure, AF
D	ACE inhibitor or ARB	All patients unless contraindicated or not tolerated
	β-Blocker	Stable NYHA class IV
	Diuretics	Fluid retention
	Digoxin	AF with rapid ventricular response
	Positive inotropes	Bridge to transplant or end of life

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; MI, myocardial infarction; LVD, left ventricular dysfunction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association.

improvement in symptoms and in the survival rate. In contrast, drugs that have been shown to activate neurohormonal pathways (e.g., oral positive inotropes) have a neutral or adverse effect on long-term survival.

A third concept that has evolved from randomized clinical trials is that all therapeutic interventions must be critically examined with respect to two different but equally important endpoints: an improvement in symptoms or quality of life and an improvement in survival. Although it is preferable that all interventions have a concordant effect on these endpoints, this is not always the case (Table 14–1). For example, diuretics are very effective in reducing signs and symptoms of heart failure, but their effects on survival are unknown. In contrast, β-blockers reduce hospitalizations and prolong survival, but their effects on exercise tolerance and quality of life are less evident. The distinction between the two endpoints is also reflected in prioritization of treatment for different patient subgroups. For example, patients with asymptomatic left ventricular dysfunction do not require therapy that will reduce symptoms, but they benefit from treatment that slows disease progression and prolongs life. In contrast, a patient with advanced heart failure is benefited by any treatment that relieves symptoms at the end of life.

In 2001, the writing committee of the ACC/AHA guidelines proposed a new approach to the classification of heart failure that emphasized both the development and progression of the disease.[4] Stage A and B patients are at high risk for developing heart failure. Stage A patients are those without

structural heart disease, and stage B patients are those with structural heart disease, but without signs or symptoms of heart failure. Stage C and D patients have structural heart disease with earlier or current symptoms of heart failure (stage C) or refractory heart failure requiring specialized interventions (stage D) (see Fig. 13–1 for examples). This staging system recognizes that (1) there are established risk factors and structural prerequisites for the development of heart failure; (2) therapies employed before left ventricular dysfunction or symptoms develop can reduce morbidity and mortality rates; (3) patients are expected to progress from one stage to the next unless slowed by treatment; and (4) all patients benefit from risk factor management including blood pressure control, lipid management, exercise, and smoking cessation. In this chapter, we focus primarily on stage C patients with reduced ejection fraction for whom there is a large base of evidence on which to guide therapy (Table 14–2). By contrast, a more limited discussion of empiric recommendations for patients with heart failure and normal ejection fraction is presented.

DIURETICS AND SODIUM RESTRICTION

Pathophysiologic Mechanisms

A common abnormality in patients with heart failure is an expanded extracellular volume that is characterized by pulmonary congestion, peripheral edema, ascites, elevated jugular venous pulse, and symptoms such as ankle swelling, dyspnea on exertion, and orthopnea. These abnormalities are related in part to avid sodium retention by the kidney, which is caused by a complex interaction among decreased cardiac output and renal perfusion, redistribution of intrarenal blood flow to the sodium conserving medulla, systemic and local neurohormonal activation, and increased renal sympathetic nerve activity.[8] Diuretics are a cornerstone in the pharmacologic management of patients with signs and symptoms related to an expanded extracellular volume. Although restriction of dietary sodium intake is universally recommended for patients with heart failure who are treated with diuretics, this recommendation is inadequately implemented in many clinical settings. The failure to correctly implement a sodium-restricted diet diminishes the effectiveness of diuretics, increases the dosage requirement, and aggravates potassium loss.

Sodium Restriction

There are few studies that specifically assess the effect of dietary sodium intake in heart failure. Cody and coworkers[9] studied 10 patients with severe heart failure who were monitored in a clinical research center after all vasodilator and diuretic therapy was discontinued during a diet containing a very low (approximately 200 mg/day) or a moderate (approximately 2000 mg/day) sodium intake. The very low-sodium diet was associated with a significant reduction in weight, in mean pulmonary artery pressure, and in mean pulmonary capillary wedge pressure. By contrast, a high-salt diet in patients with mild heart failure has been shown to increase left ventricular volumes, suppress renin and aldosterone concentrations, and reduce daily sodium excretion.[10] Thus, even in patients without signs or symptoms of congestion, there is a reduced ability to excrete a sodium load. Other studies in patients with hypertensive heart disease[11,12] and heart failure with preserved systolic function[13] suggest that sodium restriction may reduce natriuretic peptides, attenuate ventricular remodeling, and improve clinical status.

Table 14–3 High-Sodium Containing Foods

Food	Portion	Sodium (mg)
American cheese	1 oz	406
Tuna, canned	3 oz	288
Ham	3 oz	1114
Hot dog	1	639
Spaghetti, canned	8 oz	1124
Bread, white	1 slice	114
Corn chips	2 oz	462
Chicken noodle soup	1 cup	1107
Beans, canned	1 cup	326
Soy sauce	1 tbsp	1029
Italian dressing	1 tbsp	116
Big Mac	1	1010

The recommended level of sodium restriction depends on the history and severity of edema formation. In patients with asymptomatic left ventricular dysfunction, judicious sodium restriction to no more than 3500 mg/day is probably useful. Patients with mild heart failure typically require restriction to less than 2500 mg/day, whereas those with moderate-to-severe heart failure should reduce intake to less than 2000 mg/day. Important principles include substituting herbs and other spices for table salt, avoiding common foods that contain large amounts of sodium (Table 14–3), reading food labels carefully, and cooking with fresh meats and vegetables. Keys to compliance are patient and family education by nurse specialists, referral to nutritionists, and use of patient-oriented texts and websites (e.g., *www.hfsa.org*).[14]

DIURETICS

Mechanisms of Action

Diuretics inhibit sodium reabsorption in the kidney, thereby leading to increased urinary sodium and water excretion.[15] There are several available diuretics (Table 14–4) that are usually classified according to their site of action in the kidney. Thiazide diuretics inhibit the sodium-chloride symporter in the distal convoluted tubule where approximately 5% to 10% of the filtered load of sodium is reabsorbed. As cardiac function and renal perfusion decrease, proximal tubular sodium reabsorption increases to 80% to 90% of the filtered load, making thiazide diuretics less effective. Therefore, for most patients with heart failure and edema, a loop diuretic is the preferred initial agent. Loop diuretics inhibit the sodium-potassium-chloride symporter in the thick ascending limb of the loop of Henle, leading to a marked increase in the fractional excretion of sodium. In addition, loop diuretics inhibit solute concentration in the medullary interstitium, thereby

Table 14–4 Diuretic Therapy in Heart Failure

Generic Name	Usual Oral Dose	Duration of Action (h)
Loop Diuretics		
Furosemide	40-160 mg/day	6-8
Bumetanide	0.5-4 mg/day	4-6
Torsemide	5-20 mg/day	1-4
Ethacrynic acid	50-150 mg/day	6-8
Thiazide and Thiazide-Like Diuretics		
Chlorothiazide	500-1000 mg/day	6-12
Hydrochlorothiazide	50-100 mg/day	>12
Metolazone	2.5-10 mg/day	24-48
Chlorthalidone	100 mg/day	24
Indapamide	1.25-5 mg/day	24
Potassium-Retaining Diuretics		
Spironolactone	25-100 mg/day	3 days after starting
Triamterene	100-200 mg/day	12-16
Amiloride	5-10 mg/day	24

decreasing the driving force for water reabsorption in the collecting duct. Because both loop diuretics and thiazides also cause potassium excretion, adjunctive therapy with potassium-retaining diuretics that act in the distal tubule and collecting duct may be required to maintain normokalemia. For a detailed discussion of the pharmacology of diuretics, see Chapter 23 in HD7e.

Adverse Effects

Despite the wide acceptance of diuretics, they have a number of long-term adverse effects such as electrolyte depletion, neurohormonal activation, hypotension, and renal insufficiency. Chronic diuretic therapy can result in hypokalemia, hyponatremia, hypocalcemia, and hypomagnesemia, as well as metabolic alkalosis. Hypokalemia and hypomagnesemia are of particular concern because they can precipitate arrhythmias in patients with heart failure. In addition to electrolyte depletion, diuretics may cause an increase in uric acid levels and contribute to the development of gout. An adverse effect of diuretics that may be particularly important in patients with heart failure is activation of neurohormonal pathways.[16,17] The mechanisms by which diuretics stimulate renin and norepinephrine release have not been completely defined,[18] but there are three important pathophysiologic consequences. First, renin secretion will result in increased secretion of aldosterone, which will promote sodium retention. Second, increased vasoconstriction secondary to increased levels of angiotensin II and norepinephrine may have a positive feedback effect in which the increased impedance to ventricular emptying results in progressive ventricular dysfunction. Third, norepinephrine, angiotensin II, and aldosterone exert direct toxic effects on the myocardium, resulting in ventricular remodeling and proarrhythmia. Finally, neurohormonal activation is a strong predictor of increased mortality.[19,20] Therefore, it is possible, although unproven, that diuretic-associated neurohormonal stimulation could be associated with an adverse effect on long-term survival.

The association of diuretic therapy with neurohormonal activation has an important influence on the optimal use of diuretics for patients with heart failure. As discussed, it is useful to reinforce dietary sodium restriction in patients who appear to require large doses of diuretics. Second, it is important to emphasize that many of the adverse effects of neurohormonal stimulation by diuretics can be blocked by the concomitant administration of an ACE inhibitor and β-blocker. With combination therapy, the beneficial effect of diuretics may be obtained, but the increase in angiotensin II and aldosterone will be blocked and the effects of norepinephrine will be inhibited. It is also important to understand the effects of secondary processes that can cause overall sodium balance to return to neutral, despite continued diuretic administration. The response to a diuretic-induced reduction of extracellular volume is a further reduction in sodium and chloride excretion through stimulation of proximal tubular reabsorption, increased renal sympathetic nerve activity, and increased aldosterone.[21] Chronic diuretic treatment induces a number of changes in the collecting duct and distal tubule, including increases in mitochondrial volume and adenosine triphosphatase activity, and cellular hypertrophy, that increase distal tubular reabsorption.[22]

The pharmacokinetic and pharmacodynamic effects of diuretics may be abnormal in patients with heart failure.[15] In patients with bowel wall edema and splanchnic hypoperfusion, the absorption of orally administered drugs can be reduced, thereby delaying the time to appearance and peak concentration of the diuretic in the urine. Unless the glomerular filtration rate is less than 30 mL/min, the pharmacokinetics of intravenous formulations are largely normal in heart failure, which explains the effectiveness of the intravenous route in patients with decompensated heart failure (see Chapter 17). The pharmacodynamic response is reduced in heart failure, so that the rate of sodium excretion is reduced at any given renal tubule diuretic concentration.[15] Thus, the "ceiling" dose, or dose above which further sodium excretion is minimal, is typically double in patients with heart failure

compared with normal subjects. For this reason, prescribing a larger dose of diuretic is commonly more effective than increasing the frequency of administration.

Practical Considerations

Short-term studies have shown that diuretics reduce signs and symptoms of congestion and lower cardiac filling pressures within hours to days of initiation; intermediate-term studies demonstrate the beneficial effects of diuretics on exercise tolerance and quality of life. The effects of diuretics on morbidity and mortality rates in heart failure have not been tested. According to ACC/AHA guidelines, diuretics should be prescribed to all patients with current or prior symptoms of heart failure who have evidence of fluid retention, and should be combined with an ACE inhibitor and β-blocker to maintain clinical stability.[4] The first step is to identify patients with fluid retention based on symptoms (shortness of breath, orthopnea, paroxysmal nocturnal dyspnea), signs (rales, elevated jugular venous pulse, peripheral edema), and other clinical characteristics such as weight gain, frequent outpatient visits, or recurrent hospitalizations. Noninvasive studies that may be helpful in recognizing hypervolemia include chest radiography, natriuretic peptide levels, and echocardiography, although the sensitivity and specificity of these tests are limited.[23] Newer devices, such as implantable hemodynamic and intrathoracic impedance monitors[24,25] and noninvasive Valsalva response recorders,[26] have also been developed for use in heart failure. Direct assessment of blood volume using a radiolabeled albumin technique is available at specialized centers.[27] If the clinical evaluation is equivocal, a right heart catheterization to measure intracardiac filling pressures should be considered.

For patients with heart failure, the most commonly prescribed loop diuretic is furosemide, which is usually started at a low dose (20 to 40 mg once daily) and increased until urine output increases and weight loss occurs. The dose or frequency of diuretics may be titrated while monitoring several endpoints. Because one of the primary goals of therapy is symptom relief, the dose of diuretics may be reduced to maintenance levels once there are satisfactory reductions in dyspnea, orthopnea, and edema. Attention to normalizing the jugular venous pulse and eliminating congestive hepatomegaly is key to achieving euvolemia, especially in patients with advanced heart failure. The development of symptomatic hypotension or azotemia often necessitates holding diuretic therapy, but diuretics can often be resumed at a lower dose after adjustment of other heart failure medications such as ACE inhibitors and β-blockers. Once fluid retention has resolved, a maintenance dose of diuretics is recommended to prevent recurrent volume overload.[4] Select patients with mild heart failure or asymptomatic left ventricular dysfunction may not require maintenance diuretics if they were initially effective in reducing dietary sodium intake,[28] although a strategy of diuretic withdrawal has not been tested.

Some patients have refractory signs and symptoms of heart failure, and are labeled "diuretic resistant." These patients may be noncompliant with their medication regimens or unable to limit sodium and fluid intake; they require reinforcement of education. In patients with biventricular or right heart failure, significant bowel wall edema may limit oral absorption, so that intravenous formulations (e.g., furosemide or chlorothiazide) or loop diuretics with increased oral bioavailability (e.g., torsemide)[29] may be effective in initiating a diuresis. In patients with low cardiac output, the problem is inadequate sodium delivery to the tubular lumen caused by reduced renal perfusion and impaired tubular secretion of diuretics. Most patients will respond to a doubled dose rather than to the same dose taken twice daily.

In other patients, the combination of a loop diuretic with a thiazide diuretic or metolazone, which facilitates the action of the loop diuretic, may be particularly effective.[30] The mechanisms of diuretic synergism are not fully defined but are likely related to the fact that diuretics inhibit transport in different segments of the nephron. Adding a thiazide diuretic may inhibit "compensatory" distal tubular adaptations, and may result in a sustained diuresis that would be much greater than simply increasing the dose of the loop diuretic. The addition of metolazone may also be used for transient episodes of fluid accumulation. This strategy maintains the dose of the loop diuretic constant, minimizes errors associated with frequent dose changes, and reduces the long-term exposure to high-dose diuretics. Close monitoring is required because this "booster" pill strategy can lead rapidly to overdiuresis, hypokalemia, and renal insufficiency.

During long-term treatment, and particularly during changes in diuretic regimens, it is important to monitor levels of potassium, given the marked kaliuretic effects of diuretic drugs. Renal function, as assessed by serum blood urea nitrogen and creatinine levels, should be monitored because this parameter may be sensitive to changes in blood volume and/or vasoconstrictor hormones. Excessive volume depletion should be avoided because it may result in hypotension and renal dysfunction. In patients with coexistent heart failure and chronic kidney disease (so-called "cardiorenal syndrome"),[31] potential nephrotoxic agents should be used with extreme caution. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors should be avoided because these agents can inhibit the natriuretic effects of diuretics and impair renal function, thereby exacerbating fluid retention. Other agents such as thiazolidinediones[32] and pregabalin[33] that cause edema are relatively contraindicated in heart failure.

Patients should weigh themselves on a daily basis. If they do not own a scale, one should be provided for them. This process helps to engage patients in their medical care, alert them to the effect of dietary indiscretions, and facilitate "fine tuning" of medications. For select patients, electronic scales that transmit daily information on weight, vital signs, and symptoms may help to maintain accuracy and compliance. In the case of a rapid weight gain of 2 to 3 pounds, a temporary increase in diuretic dosage or the addition of metolazone or a thiazide diuretic for 1 to 3 days, is often sufficient to return the patient to "dry weight." In patients with advanced heart failure, it is important to remember that dry weight may decrease over time with loss of skeletal muscle mass and adipose tissue due to cardiac cachexia.[34] The use of intravenous diuretics and other fluid management strategies in hospitalized patients with decompensated heart failure are discussed in Chapter 17.

RENIN-ANGIOTENSIN SYSTEM INHIBITORS

Pathophysiologic Mechanisms

Nearly 30 years ago, an important advance in the treatment of heart failure was the recognition that pump function is critically dependent on the outflow resistance against which the ventricle must empty.[35] Acute hemodynamic studies established that vasodilator drugs that relax peripheral arterioles shift the ventricular function curve upward and to the left, resulting in an increase in cardiac output without a large change in blood pressure. Moreover, drugs that increase venous capacitance redistribute blood volume from the central to peripheral reservoirs and, therefore, decrease the signs and symptoms of elevated cardiac filling pressures. Unlike hydralazine, that acts predominantly on the arterioles leading to a reduction in impedance or nitrates that, in turn, act on arterial compliance and venous tone, ACE inhibitors have a balanced effect on arterioles, arteries, and veins.

The traditional view of ACE inhibitors was that their primary mechanism of action in heart failure was a reduction in angiotensin II-mediated vasoconstriction. The reduction of angiotensin II was noted to decrease the release of aldosterone from the adrenal gland and norepinephrine in the synaptic cleft.[36] Subsequent studies showed that the actions of ACE inhibitors are considerably more complex than a simple effect on circulating levels of angiotensin II (Fig. 14–2). Because kininase is identical to converting enzyme, ACE inhibitors also reduce the metabolism of bradykinin. Bradykinin can stimulate the release of nitric oxide and other endothelium-dependent vasodilators including prostaglandins. More importantly, by inhibiting tissue renin-angiotensin systems in blood vessels, the kidney, and the heart, ACE inhibitors play a critical role in attenuating vascular and myocardial remodeling, reducing inflammation and the risk of thrombosis, and delaying the progression of renal disease. All of these actions have an important impact on mediating the clinical efficacy of ACE inhibitors in heart failure.

Several nonenzymatic pathways independent of ACE exist for the conversion of angiotensin I to angiotensin II and may contribute to persistent availability of both circulating and tissue angiotensin despite treatment with ACE inhibitors (see Fig. 14–2).[36] This "escape" phenomenon may be due, in part, to non-ACE pathways of angiotensin I metabolism (e.g., myocardial chymase) and provides the rationale for the development of angiotensin receptor blockers.[37] The angiotensin receptor blockers bind competitively to, and dissociate slowly from, angiotensin II type 1 receptors.[38] Circulating angiotensin II levels increase during therapy due to loss of negative feedback. There are two angiotensin receptor blockers approved for the treatment of heart failure (Table 14–5). Valsartan is approved for the treatment of patients with NYHA functional class II-IV heart failure and indicated to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or dysfunction following myocardial infarction. Candesartan is indicated to reduce the rate of cardiovascular mortality and the number of hospitalizations in patients with NYHA functional class II-IV heart failure and reduced ejection fraction.

Clinical Efficacy

ACE Inhibitors

Numerous prospective, placebo-controlled studies have shown the beneficial effects of ACE inhibitors on exercise tolerance, salt and water balance, clinical signs and symptoms, neurohormonal stimulation, quality of life, and survival in patients with chronic heart failure (Table 14–6). The concordance of findings in these multicenter trials provides a strong scientific basis for the use of ACE inhibitors in the management of heart failure. Several multicenter trials deserve comment.

Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

CONSENSUS randomized 253 hospitalized patients with New York Heart Association (NYHA) functional class IV

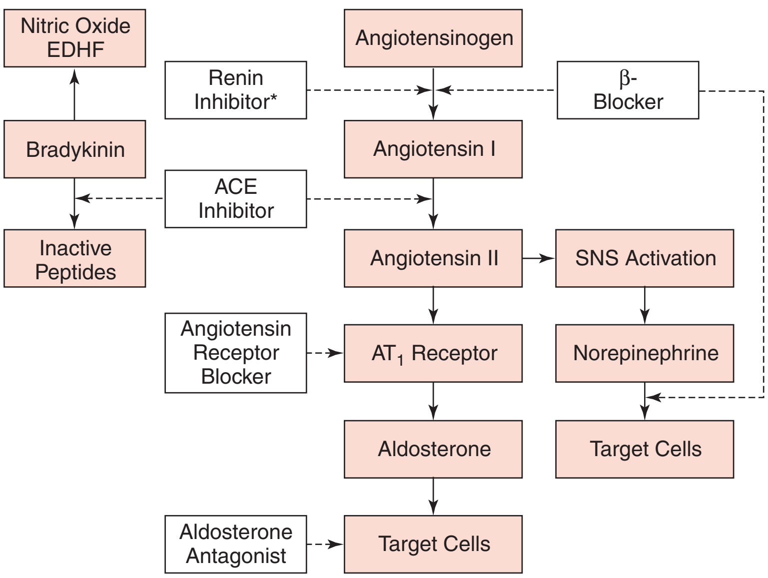

Figure 14–2 Pharmacologic agent (*open boxes*) used to manipulate the renin-angiotensin-aldosterone system (*shaded boxes*). *Dashed lines* signify inhibitory pathways. *Asterisk* denotes investigational agents. EDHF, endothelium-derived hyperpolarizing factor; SNS, sympathetic nervous system. (Adapted from Givertz MM: Manipulation of the renin-angiotensin system. Circulation 2001;104:e14-e18, with permission.)

symptoms to either enalapril or placebo in addition to treatment with digoxin, diuretics, and non-ACE vasodilators.[39] Based on an interim analysis, enalapril was associated with a highly significant survival benefit compared with placebo (52% versus 36%), although there was no difference in the combined risk of death or hospitalization for heart failure. The CONSENSUS trial was prematurely terminated, because it was deemed unethical to continue a trial in which one half of the participants was randomized to placebo.

Vasodilator Heart Failure Trial (V-HeFT) II

V-HeFT I was the first placebo-controlled trial to demonstrate that vasodilators could prolong survival in patients with heart failure.[40] V-HeFT II was designed to compare treatment with hydralazine-isosorbide dinitrate, which was the superior drug combination in V-HeFT I, to enalapril, in patients with mild-to-moderate heart failure due to ischemic or nonischemic cardiomyopathy.[41] The enalapril group had a lower 2-year mortality rate compared with those patients randomized to hydralazine-isosorbide dinitrate (18% versus 25%; mortality reduction, 28%; P = 0.016). Interestingly, exercise time and left ventricular function improved to a greater degree in the patients randomized to hydralazine-isosorbide dinitrate.

Studies of Left Ventricular Dysfunction (SOLVD)

SOVLD was a prospective, double-blind, placebo-controlled trial in patients with an ejection fraction of 35% or less.[42] The SOLVD Treatment Trial randomized 2569 patients with NYHA functional class II or III heart failure, treated with digitalis and diuretics, to enalapril or placebo. After a mean follow-up of 41 months, there were significantly more deaths in the placebo group compared with the enalapril group (510 versus 452; mortality reduction, 16%; P = 0.0036). Furthermore, enalapril was associated with a 30% reduction in hospitalizations for heart failure.

The SOLVD Prevention Trial[43] was run concurrently with the Treatment Trial and used the same experimental design except for the restriction to patients with no or minimal symptoms of heart failure who were on no treatment for overt heart failure. After an average follow-up of 37 months, there were 334 deaths in the placebo group compared with 313 in the enalapril group. This 8% mortality reduction approached, but did not achieve, statistical significance (P = 0.30). More impressive were the highly significant reductions in the first hospitalization for heart failure (36%) and in the onset of heart failure requiring pharmacologic therapy (37%).

Assessment of Treatment with Lisinopril and Survival (ATLAS)

Despite controlled trials demonstrating the benefits of high-dose ACE inhibitor therapy (e.g., captopril 50 to 100 mg three times daily, enalapril 10 to 20 mg twice daily), much lower doses are used in clinical practice owing to concerns regarding patient tolerance. The ATLAS study[44] randomized 3164 patients with NYHA functional class II-IV heart failure and an ejection fraction of 30% or less to low-dose (2.5 to 5 mg daily) or high-dose (32.5 to 35 mg daily) lisinopril. After a median follow-up of 46 months, high-dose lisinopril was modestly superior in decreasing the combined risk of death or hospitalization (12% reduction, P = 0.0002), but had no significant effect on all-cause mortality. Dizziness and renal insufficiency were more common in the high-dose group, but the rate of

Table 14–5 ACE Inhibitor, Angiotensin Receptor Blocker and β-Blocker Therapy in Heart Failure with Low Ejection Fraction

Generic Name	Initial Daily Dose	Maximum Dose
ACE Inhibitors		
Captopril	6.25 mg tid	50 mg tid
Enalapril	2.5 mg bid	10-20 mg bid
Fosinopril	5-10 mg qd	40 mg qd
Lisinopril	2.5-5 mg qd	20-40 mg qd
Quinapril	5 mg bid	20 mg bid
Ramipril	1.25-2.5 mg qd	10 mg qd
Trandolapril	1 mg qd	4 mg qd
Angiotensin Receptor Blockers		
Candesartan	4-8 mg qd	32 mg qd
Losartan	12.5-25 mg qd	100 mg qd
Valsartan	40 mg bid	160 mg bid
β-Blockers		
Bisoprolol	1.25 mg qd	10 mg qd
Carvedilol	3.125 mg bid	25 mg bid
Metoprolol CR/XL	12.5-25 mg qd	200 mg qd

bid, twice a day; qd, every day; tid, three times a day.
Adapted from Hunt SA, Abraham WT, Chin MH, et al: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. Circulation 2005;112:e154-e235.

Table 14–6 Randomized Controlled Trials of ACE Inhibitors and Angiotensin Receptor Blockers

Trial	*N*	Agent	Entry Criteria	Follow-Up Period	Primary Endpoint	Findings
Heart Failure Trials						
CONSENSUS[39]	253	Enalapril vs. placebo	NYHA IV	188 days	Death	Placebo 52% Enalapril 36% (40% ↓)
V-HeFT II[41]	804	Hydralazine/ isosorbide-dinitrate vs. enalapril	CTR > 0.55 LVID > 2.7 cm/m^2 LVEF < 45% VO_2 < 25 mL/kg/min	2.5 years	Death	Hyd/ISDN 25% Enalapril 18% (28% ↓)
SOLVD Treatment[42]	2569	Enalapril vs. placebo	LVEF ≤ 35% NYHA II-III	41 mo	Death	Placebo 40% Enalapril 35% (16% ↓)
SOLVD Prevention[43]	4228	Enalapril vs. placebo	LVEF ≤ 35% No or minimal symptoms	37 mo	Death	Placebo 16% Enalapril 15% (8% ↓, *P* = 0.30)
ATLAS[44]	3164	High-dose vs. low-dose lisinopril	LVEF ≤ 30% NYHA II-IV	39-58 mo	Death	Low-dose 45% High-dose 43% (8% ↓, *P* = 0.13)
ELITE-II[47,72]	3152	Losartan vs. captopril	Age ≥ 60 years LVEF ≤ 40% NYHA II-IV	1.5 yr	Death	Losartan 18% Captopril 16% (13% ↓, *P* = 0.16)
Val-HeFT[49]	5010	Valsartan vs. placebo	LVEF < 40% LVID > 2.9 cm/m^2 NYHA II-IV	23 mo	Death Death and complications	Placebo 19% Valsartan 20% (*P* = 0.80) Placebo 32% Valsartan 29% (13% ↓)
CHARM-Added[50]	2548	Candesartan vs. placebo	LVEF ≤ 40% NYHA II-IV Treatment with ACE inhibitors	41 mo	CV death or HF hospitalization	Placebo 42% Candesartan 38% (15% ↓)
CHARM-Alternative[51]	2028	Candesartan vs. placebo	LVEF ≤ 40% NYHA II-IV Intolerance to ACE inhibitors	34 mo	CV death or HF hospitalization	Placebo 40% Candesartan 33% (23% ↓)
CHARM-Preserved[217]	2028	Candesartan vs. placebo	LVEF > 40% NYHA II-IV	37 mo	CV death or HF hospitalization	Placebo 24% Candesartan 22% (11% ↓, *P* = 0.12)
Post-infarction Trials						
SAVE[218]	2231	Captopril vs. placebo	LVEF ≤ 40% 3-16 days after MI	42 mo	Death	Placebo 25% Captopril 20% (19% ↓)
CONSENSUS II[55]	6090	Enalapril IV/PO vs. placebo	24 h after MI	6 mo	Death	Placebo 10% Enalapril 11% (10% ↑, *P* = 0.26)
AIRE[219]	2006	Ramipril vs. placebo	HF 3-10 days after MI	15 mo	Death	Placebo 23% Ramipril 17% (27% ↓)

Table 14–6 Randomized Controlled Trials of ACE Inhibitors and Angiotensin Receptor Blockers—cont'd

Trial	N	Agent	Entry Criteria	Follow-Up Period	Primary Endpoint	Findings
Post-infarction Trials—cont'd						
GISSI-3[220]	19,394	Lisinopril vs. placebo	24 h after MI	6 wk	Death	Placebo 7.1% Lisinopril 6.3% (12% ↓)
SMILE[56]	1556	Zofenopril vs. placebo	24 h after MI	6 wk	Death or severe heart failure	Placebo 10.6% Zofenopril 7.1% (34% ↓)
TRACE[221]	1749	Trandolapril vs. placebo	LVEF ≤ 35% 3-7 days after MI	4 yr	Death	Placebo 42% Trandolapril 35% (22% ↓)
ISIS-4[222]	58,050	Captopril vs. placebo	24 h after MI	5 wk	Death	Placebo 7.7% Captopril 7.2% (7% ↓)
VALIANT[57]	14,808	Valsartan vs. valsartan plus captopril vs. captopril	0.5-10 days after MI HF, LVEF ≤ 35% or both	25 mo	Death	Valsartan 20% Valsartan plus captopril 19% Captopril 20%

ACE, angiotensin-converting enzyme; AIRE, Acute Infarction Ramipril Efficacy; ATLAS, Assessment of Treatment with Lisinopril And Survival; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; CONSENSUS, COoperative North Scandinavian ENalapril SUrvival Study; CTR, cardiothoracic ratio; CV, cardiovascular; GISSI-3, Grupo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico; HF, heart failure; ISIS-4, Fourth International Study of Infarct Survival; LVEF, left ventricular ejection fraction; LVID, left ventricular internal diameter at diastole; MI, myocardial infarction; NYHA, New York Heart Association functional class; SAVE, Survival And Ventricular Enlargement; SMILE, Survival of Myocardial Infarction Long-term Evaluation; SOLVD, Studies Of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation; Val-HeFT; Valsartan in Heart Failure Trial; VALIANT, Valsartan in Acute Myocardial Infarction; V-HeFT, Vasodilator Heart Failure Trial; ↓, reduction; ↑, increase.

drug withdrawal due to adverse effects (18%) was similar in the two groups.

Angiotensin Receptor Blockers

In early clinical studies in patients with chronic heart failure caused by left ventricular systolic dysfunction, angiotensin receptor blockade produced beneficial hemodynamic effects and was generally well tolerated.[45] The Evaluation of Losartan in the Elderly (ELITE) I study randomly assigned 722 patients aged 65 years or older with NYHA functional class II through IV heart failure and an ejection fraction of 40% or less to receive losartan or captopril for 48 weeks.[46] Although there was no difference between the drugs with regard to the primary safety endpoint (i.e., treatment effect on renal function), losartan unexpectedly decreased mortality by 46%. With a design similar to ELITE I, but powered to detect a difference in all-cause mortality, ELITE II randomized 3152 patients with mild-to-moderate heart failure to losartan (target dose 50 mg once daily) or captopril (target dose 50 mg three times daily) and demonstrated a nonsignificant 13% reduction in mortality in favor of captopril.[47,72] There were also trends in favor of ACE inhibitor therapy for the secondary endpoint of sudden cardiac death and the combined endpoint of death and hospitalization. Fewer patients randomized to losartan discontinued therapy due to side effects (9% versus 15%, $P < 0.001$). The inferiority of losartan in ELITE II was likely attributable to under-dosing. Although losartan is not approved for the treatment of heart failure, the recommended daily dose in this setting is 100 mg.

There is a theoretical reason to suggest that combined therapy with an angiotensin receptor blocker and an ACE inhibitor would be more clinically effective than therapy with either alone, and this thesis has been tested in several clinical trials. In one small study, 33 patients with NYHA functional class III to IV heart failure on maximally tolerated doses of ACE inhibitors were randomized to receive adjunctive therapy with placebo or losartan for 6 months.[48] The addition of losartan was associated with a lower NYHA class and higher peak exercise oxygen consumption. The Valsartan in Heart Failure Trial (Val-HeFT) randomized 5010 patients with NYHA functional class II-IV heart failure to receive valsartan (target dose 160 mg twice daily) or placebo in addition to usual therapy that included ACE inhibitors in 93% and β-blockers in 36%.[49] Valsartan significantly reduced the combined endpoint of mortality and morbidity by 13% ($P = 0.009$), including a 28% reduction in heart failure hospitalization, but exerted a neutral effect on all-cause mortality. Despite post-hoc analysis that raised concern about adverse outcomes in patients who received an ACE inhibitor, angiotensin receptor blocker and β-blocker (so-called "triple therapy"), the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added study reported similar efficacy results, as well as safety.[50] In

CHARM-Added, 2548 patients with mild-to-moderate heart failure and reduced ejection fraction who were being treated with ACE inhibitors were randomized to receive candesartan (target dose 32 mg once daily) or placebo. During a median follow-up of 41 months, candesartan reduced the combined endpoint of cardiovascular death or heart failure hospitalizations by 15% ($P = 0.01$). Importantly, candesartan reduced this risk in patients treated with β-blockers in addition to an ACE inhibitor, and was as effective among patients taking a recommended dose of ACE inhibitor as in those taking lower doses. The risks of worsening renal function and hyperkalemia were higher, however, with "add on" therapy.

For patients who are intolerant of ACE inhibition, angiotensin receptor blockade has proven effective as alternative therapy. In the CHARM-Alternative study, 2028 patients with symptomatic left ventricular dysfunction who were not receiving ACE inhibitors because of cough (72%), hypotension (13%), or renal dysfunction (12%) were randomized to receive candesartan (target dose 32 mg once daily) or placebo.[51] During a median follow-up period of 34 months, candesartan reduced the risk of cardiovascular death or heart failure hospitalization by 23% ($P = 0.004$). In addition, there was a trend toward a decrease in all-cause mortality with candesartan (hazard ratio, 0.87; 95% CI, 0.74 to 1.03; $P = 0.11$). A subgroup of 366 patients in the Val-HeFT study who were not taking ACE inhibitors at baseline also experienced a significant reduction in the rates of morbidity and mortality with angiotensin receptor blockade.[49]

In addition to targeting patients with heart failure, several large trials have studied the effects of ACE inhibitors and angiotensin receptor blockers on mortality in patients after acute myocardial infarction (see Table 14–6).[52] These trials focused on a patient population that is not comparable with patients with chronic heart failure and reduced ejection fraction who were enrolled in the V-HeFT, CONSENSUS, SOLVD, and CHARM trials. In addition, background drug therapy and study drug dosing differed significantly from the chronic heart failure trials. Nevertheless, the results of the post-infarction trials have several important implications when considering treatment for patients with left ventricular systolic dysfunction and/or heart failure.

First, the majority of these trials showed that treatment with an ACE inhibitor initiated early after myocardial infarction had a small but significant benefit in reducing short-term mortality. This finding is significant because most of the patients enrolled in the post-infarction trials did not have heart failure. Furthermore, the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated a reduction in mortality from the ACE inhibitor, ramipril, in patients with atherosclerosis in the absence of heart failure,[53] and the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) confirmed the vasculoprotective effect of ACE inhibitors in even lower risk patients.[54]

A second and more compelling issue is that early intervention with an ACE inhibitor can prevent, or at least delay, the onset of heart failure. In the SAVE trial[218] captopril was associated with a 37% reduction in the development of heart failure and a 22% reduction in hospitalizations for heart failure. In CONSENSUS II, enalapril reduced the need to change therapy for heart failure by 10%,[55] and in the Survival of Myocardial Infarction Long-term Evaluation (SMILE) study, early use of zofenopril reduced the likelihood of developing severe heart failure within 6 weeks of the infarction.[56] These data are consistent with the results of the SOLVD Prevention Trial, wherein a 20% reduction in hospitalizations for heart failure and a 29% reduction in the development of heart failure were found. In the HOPE study, ramipril reduced the risk of developing heart failure by 23%; and in EUROPA, perindopril reduced heart failure hospitalizations by 39%. These cumulative data suggest that ACE inhibitors have a significant clinical benefit, even in relatively low-risk patients.

Third, results from the Valsartan in Acute Myocardial Infarction (VALIANT) trial[57] suggest that, although ACE inhibitors and angiotensin receptor blockers are equally effective at reducing the rates of morbidity and mortality in patients with acute myocardial infarction and heart failure, left ventricular systolic dysfunction or both, combined therapy offers no advantages over ACE inhibition or angiotensin receptor blockade alone and increases the rate of adverse events.[57] These findings appear to be at odds with results from the Val-HeFT and CHARM studies demonstrating further cardiovascular risk reduction with the addition of angiotensin receptor blockade to background ACE inhibition. However, differences in patient population, drug regimens, and patterns of cardiovascular risk among patients with stable heart failure and those with acute myocardial infarction likely explain these divergent results.[57]

Practical Considerations

ACE Inhibitors

Despite the overwhelming database from clinical trials and the adoption of consensus guidelines, the application (including usage and dosing) of ACE inhibitors to the broad population of patients with chronic heart failure remains suboptimal. Several factors are responsible for this. First, the use of ACE inhibitors appears to vary among different specialties, as evidenced by the fact that cardiologists are more likely to prescribe ACE inhibitors than are primary care physicians.[58] Second, it is a common perception that ACE inhibitors are associated with a high frequency of adverse effects when used at higher doses and/or in the elderly. However, the early experience from CONSENSUS and SOLVD in a large population of ambulatory patients suggested that the incidence of these complications is acceptably low, given the potential benefit, and ATLAS demonstrated no increased risk of drug withdrawal with high-dose therapy.[44] The management and avoidance of ACE inhibitor-related complications can be facilitated by the knowledge of certain predisposing factors and by the institution of precautionary measures. Other patient-related factors associated with physician underuse of ACE inhibitors include older age, renal dysfunction, and preserved systolic function.[59]

The most important adverse effect to monitor during the initiation of ACE inhibitors is hypotension (Table 14–7), although the decrease in blood pressure is usually minor and the patient is asymptomatic. Patients who are at highest risk for symptomatic hypotension are those who are volume depleted, receiving high doses of diuretics or concomitant vasodilator therapy, or older than 75 years. Patients with increased activation of the renin-angiotensin-aldosterone

Table 14–7 Adverse Effects of Renin-Angiotensin-Aldosterone System Inhibitors

Adverse Effect	ACE Inhibitor	Angiotensin Receptor Blocker	Aldosterone Antagonist
Hypotension	++	++	+
Renal insufficiency	++	++	+/−
Hyperkalemia	+	+	++
Cough	+	−	−
Angioedema	++	+	−
Skin rash	+	+/−	−
Neutropenia	+	+	+/−
Gynecomastia	−	−	+

ACE, angiotensin-converting enzyme.

system, manifest by increased levels of plasma renin activity, are those who have angiotensin-mediated vasoconstriction and who are also at risk for hypotension.[60] Because measurements of plasma renin activity are not readily available, clinicians can take advantage of the relatively tight inverse correlation between plasma renin activity and serum sodium.[61] Patients with a low serum sodium (<130 mmol/L) are more likely to develop hypotension during the initiation of therapy. Useful strategies in these patients include temporary withholding of diuretics, liberalizing salt intake, and the use of a test dose of a short-acting ACE inhibitor (e.g., captopril 6.25 mg) followed by gradual upward titration over several weeks. If symptomatic hypotension occurs with the first dose, it may not recur with subsequent dosing.

Although mild renal insufficiency may concern clinicians, there are several misconceptions regarding the effects of ACE inhibitors on renal function. Many patients with heart failure actually have an improvement in renal function with the initiation of ACE inhibitors, likely mediated by an increase in cardiac output and renal perfusion. In addition, the incidence and magnitude of renal insufficiency in controlled trials are low, and only a small percentage of patients (less than 0.5%) are withdrawn from therapy. The mechanisms that contribute to renal insufficiency are complex and are accentuated by concomitant drug therapy and hemodynamic abnormalities. Patients at risk for renal insufficiency share many of the same features as those at risk for hypotension. In general, patients should be reassessed approximately 1 week after initiation of an ACE inhibitor to monitor renal function and blood pressure. If there is an increase in serum creatinine of 0.5 mg/dL or more, the volume status and diuretic dose should be reassessed. In the majority of cases, renal function will return to baseline once volume status returns to normal or if the diuretic dose is decreased. It is also advisable to check for concomitant medications (e.g., nonsteroidal anti-inflammatory drugs) or medical conditions (e.g., renal artery stenosis) that can aggravate renal insufficiency. Despite these concerns, ACE inhibitors may slow the progression of renal disease in heart failure patients with hypertensive and/or diabetic nephropathy.[62]

Hyperkalemia can occur in patients receiving ACE inhibitors because of the reduction in angiotensin II-mediated aldosterone secretion. Elevated potassium levels are more common in patients with diabetes or chronic kidney disease, especially if they are receiving potassium supplements or potassium-retaining diuretics. Therefore, the dosage of potassium chloride and potassium levels should be monitored approximately 1 week after initiating ACE inhibitors, and potassium-retaining diuretics should be used with caution.

The other side effects of ACE inhibitors, such as dysgeusia, skin rash, and cough, are commonly self limited or reversible with discontinuation of the drug. Clinicians must be particularly cautious about stopping ACE inhibitors because of cough, which has been reported in 5% to 15% of patients in clinical studies. ACE inhibitor-related cough is typically nonproductive, arises during the first few months of therapy, and disappears within 7 to 10 days of drug withdrawal. However, cough is a common manifestation of heart failure and may respond to an increased dose of diuretics, ACE inhibitor, or both. If the cough is intolerable, a smaller dose or temporary discontinuation can be tried. In the past, many patients would tolerate a mild cough in exchange for the important improvements in survival and quality of life; however, most patients can be easily switched to an angiotensin receptor blocker with expected clinical benefits.[51]

Angioedema is a rare but potentially life-threatening complication of ACE inhibitor therapy that can occur weeks to months after drug initiation. The causal mechanism is believed to be an accumulation of bradykinin or one of its metabolites. An ACE inhibitor should not be prescribed to any patient with a history of angioedema. Furthermore, if a patient develops angioedema while taking an ACE inhibitor, the drug should be stopped immediately.

Doses of ACE inhibitors should be titrated upward over several weeks until target doses (e.g., doses that have been shown to reduce the morbidity and mortality rates in clinical trials) are achieved (see Table 14–5). The issue of the optimal dose has been controversial because it is a common impression that many patients are being treated with substantially lower doses.[63] Although results from the ATLAS study[44] argue in favor of trying to achieve high-dose ACE inhibitor therapy to reduce the risk of hospitalization, lower doses showed similar effects on symptoms and mortality. For patients who cannot tolerate high-dose ACE inhibitors, low or intermediate doses should be continued while β-blockers are initiated. Once a maximally tolerated dose of ACE inhibitor has been achieved, patients can generally be maintained on this dose long term despite changes in other heart failure medications. However, 20% to 25% of patients with advanced heart failure will develop a circulatory or renal limitation to ACE inhibitor therapy.[64] These patients tend to be older with longer duration of heart failure, lower blood pressure, and baseline renal dysfunction. ACE inhibitor intolerance is a marker of poor prognosis.

Another controversial issue is whether the beneficial effects of ACE inhibitors are class or drug specific. Currently, captopril, enalapril, lisinopril, quinapril, and fosinopril are indicated for the treatment of symptomatic heart failure. Captopril, ramipril, and trandolapril are indicated for post-myocardial infarction patients, and enalapril is the only ACE inhibitor indicated for the prevention of heart failure in asymptomatic patients. There are insufficient data to prove that the benefits demonstrated in clinical trials are applicable to all ACE inhibitors or only to the specific drug studied, but meta-analyses suggest an equivalent survival benefit for several different ACE inhibitors,[65] with consistent effects in a broad range of patients.[66] Although there are some differences in structure, pharmacokinetics, and pharmacodynamics, it is not known whether these differences have a significant impact on clinical outcomes. Furthermore, cost has become a dominant issue for many patients and providers.

There is some evidence that aspirin may attenuate the clinical benefits of ACE inhibitors by inhibiting bradykinin-mediated prostaglandin synthesis. In small pilot studies, aspirin inhibited the improvement in exercise duration and peak oxygen consumption and attenuated the hemodynamic effects of ACE inhibitors in patients with chronic heart failure.[67] Additional data from thromboembolic prevention studies also suggests that aspirin may have an adverse effect on the risk of heart failure hospitalizations.[68,69] Finally, in a post-hoc analysis of SOLVD, the survival benefit of enalapril was not seen in patients receiving antiplatelet therapy at baseline.[70] Notably, the attenuation of ACE inhibitor benefit appears less evident with clopidogrel. Current guidelines recommend aspirin use for primary and secondary prevention of myocardial infarction in patients with ischemic heart failure, yet there is no proven role for aspirin in patients with nonischemic cardiomyopathy.[68]

Angiotensin Receptor Blockers

Based on the clinical trials data and the ACC/AHA guidelines,[4] there are several indications for angiotensin receptor blockers in patients with heart failure and reduced ejection fraction. First, these agents may be used as alternative therapy in patients who are intolerant to ACE inhibitors, primarily evidenced by persistent cough. Although angiotensin receptor blockers were initially believed to be a safe alternative in patients with ACE inhibitor-induced angioedema, case reports suggest that life-threatening events may recur with the use of these agents.[71] Second, although ACE inhibitors remain the initial agents of choice for inhibition of the renin-angiotensin system, angiotensin receptor blockers are a reasonable alternative and may be better tolerated in older patients,[72] although more recent data suggest that these agents are just as likely to produce hypotension and worsening renal function as are ACE inhibitors (see Table 14–7). Based on data from Val-HeFT and CHARM-Added, the addition of an angiotensin receptor blocker should be considered to reduce heart failure hospitalizations in patients who remain symptomatic despite ACE inhibitor and β-blocker therapy. The safety of adding an angiotensin receptor blocker to patients who are already treated with both an ACE inhibitor and aldosterone antagonist is unknown.

Like ACE inhibitors, angiotensin receptor blockers should be started at low doses (see Table 14–5) and titrated upward until target doses are achieved (e.g., candesartan 32 mg once daily, losartan 50 to 100 mg once daily, valsartan 160 mg twice daily). There have been no large studies comparing efficacy and safety of high- with low-dose angiotensin receptor blockade. The risks of hypotension, renal insufficiency, and hyperkalemia are similar to those seen with ACE inhibitor monotherapy, and the guidelines regarding clinical and laboratory follow-up discussed earlier should be followed. Greater caution is warranted when angiotensin receptor blockers are added to ACE inhibitors as shown by the higher rates of adverse events that required drug withdrawal in the combined therapy group in the VALIANT study.[57]

β-BLOCKERS

Pathophysiological Rationale

β-Blockers were traditionally contraindicated in patients with heart failure owing to concerns that their negative inotropic actions could result in clinically important deterioration. It is now well established that chronic overactivity of the sympathetic nervous system plays an important role in the pathophysiology of heart failure (discussed in detail in Chapter 21 in HD7e).[73] Adverse effects of circulating catecholamines and increased cardiac adrenergic drive include (1) myocardial hypertrophy, fibrosis, and apoptosis leading to ventricular remodeling and impaired contractile function; (2) β-receptor *downregulation*, a complex sequence of biochemical and molecular events resulting in a decreased number of surface β-receptors and uncoupling of the β-receptor complex; (3) atrial and ventricular arrhythmias; (4) myocardial ischemia; (5) impaired renal sodium excretion; and (6) peripheral vasoconstriction. Regardless of the mechanism, it is clear that β-blockers cause slowing or regression of ventricular remodeling, and in doing so reduce the rate of morbidity and mortality in patients with chronic heart failure.

Pharmacology

Three classes of β-blockers are available for clinical use (see Chapters 2 and 5, and Table 23–11 in HD7e). *First-generation* agents, such as propranolol and timolol, are non-selective β-blockers with an equal affinity for β_1- and β_2-receptors. *Second-generation* β-blockers, such as metoprolol and bisoprolol, selectively inhibit β_1-receptors. *Third-generation* agents, such as carvedilol and bucindolol, were developed to include other pharmacologic properties in addition to β-blockade, in particular, vasodilation. Carvedilol is a non-selective β_1/β_2-blocker with potent α_1-blocking properties. In vitro studies also suggest that carvedilol exerts antioxidant effects,[74] although the clinical relevance of these findings remains unknown. Bucindolol is also a nonselective β-blocker with weak vasodilator properties, probably mediated via α_1-receptor blockade.[73] Nebivolol is a β_1-blocker with vasodilatory properties related to increased bioavailability of nitric oxide.[75]

Clinical Efficacy

In 1975, investigators at the University of Göteberg in Sweden first reported the beneficial effects of β-blockers, when added

to digoxin and diuretics, in patients with dilated cardiomyopathy.[76] In the 1980s and early 1990s, several small clinical trials showed that β-blockers, when administered carefully, can result in improved ventricular structure and function, hemodynamics, and β-receptor density.[77] Subsequent studies also demonstrated benefits of β-blockade on exercise tolerance and symptoms in patients with mild-to-moderate heart failure.[78] Finally, randomized controlled trials involving more than 20,000 patients with reduced ejection fraction treated with ACE inhibitors and diuretics (Table 14–8) demonstrated conclusively that β-blockers reduce hospitalizations and prolong survival in patients with chronic heart failure. As with ACE inhibitors, subgroup and meta-analyses show that β-blockers are equally effective in patients with ischemic and nonischemic heart failure, and in a broad range of patients including women, diabetics, blacks, and the elderly.[66,79,80] Several multicenter trials deserve comment.

Cardiac Insufficiency Bisoprolol Study (CIBIS) I and II

CIBIS I randomized 641 patients with ischemic or nonischemic cardiomyopathy and moderate-to-severe heart failure to either bisoprolol (up to 5 mg daily) or placebo.[81] After an average follow-up of 23 months, the total mortality rate was slightly but not significantly reduced in the bisoprolol group (17% versus 21%, $P = 0.22$). Subgroup analysis demonstrated that the mortality benefit was confined to patients with nonischemic cardiomyopathy. CIBIS II randomized 2647 patients with NYHA functional class III-IV heart failure and

Table 14–8 Randomized Controlled Trials of β-Blockers

Trial	*N*	Agent	Entry Criteria	Follow-Up Period	Primary Endpoint	Findings
CIBIS I[81]	641	Bisoprolol vs. placebo	LVEF < 40% NYHA III-IV	23 mo	Death	Placebo 21% Enalapril 17% (20% ↓, *P* = 0.22)
U.S. Carvedilol Heart Failure Trials[87]	1094	Carvedilol vs. placebo	LVEF ≤ 35% NYHA II-IV	6 mo	Death	Placebo 7.8% Carvedilol 3.2% (65% ↓)
CIBIS II[82]	2647	Bisoprolol vs. placebo	LVEF ≤ 35% NYHA III-IV	16 mo	Death	Placebo 17% Bisoprolol 12% (34% ↓)
MERIT-HF[88]	3991	Metoprolol CR/XL vs. placebo	LVEF ≤ 40% NYHA II-IV	12 mo	Death	Placebo 11% Metoprolol 7% (34% ↓)
BEST[91]	2708	Bucindolol vs. placebo	LVEF < 35% NYHA III-IV	2 yr	Death	Placebo 33% Bucindolol 30% (10% ↓, *P* = 0.10)
COPERNICUS[92]	2289	Carvedilol vs. placebo	LVEF < 25% NYHA IIIB-IV	10 mo	Death	Placebo 17% Carvedilol 11% (35% ↓)
CAPRICORN[223]	1959	Carvedilol vs. placebo	LVEF ≤ 40% 3-21 days after MI	1.3 yr	Death or CV hospitalization	Placebo 37% Carvedilol 35% (8% ↓, *P* = 0.30)
COMET[94]	3029	Carvedilol vs. metoprolol	LVEF ≤ 35% NYHA II-IV CV admission within 2 yr	58 mo	Death	Metoprolol 40% Carvedilol 34% (17% ↓)
SENIORS[98]	2128	Nebivolol vs. placebo	Age ≥ 70 years LVEF ≤ 35% or HF admission within 1 yr	21 mo	Death or CV admission	Placebo 35% Nebivolol 31% (14% ↓)

BEST, β-Blocker Evaluation and Survival Trial; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CIBIS, Cardiac Insufficiency Bisoprolol Study; COMET, Carvedilol or Metoprolol European Trial; COPERNICUS, CarvedilOl ProspectivE RaNdomized Cumulative Survival; HF, heart failure; LVEF, left ventricular ejection fraction; MERIT-HF, MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure; MI, myocardial infarction; NYHA, New York Heart Association functional class; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure; ↓, reduction.

an ejection fraction of 35% or less to bisoprolol (up to 10 mg daily) or placebo for a mean of 1.3 years.[82] The study was stopped 18 months early because bisoprolol was associated with a 34% reduction in all-cause mortality. Bisoprolol also reduced sudden death by 44% and hospitalizations by 20%. Unlike CIBIS I, the treatment effects in CIBIS II were independent of the cause of heart failure. Notably, over 90% of the patients enrolled in CIBIS II were in NYHA class III and the annualized placebo mortality was only 13%, leading the investigators to warn against extrapolating the results to patents with severe heart failure.

U.S. Carvedilol Heart Failure Trials

The U.S. Carvedilol Heart Failure Trials program enrolled 1094 patients with NYHA functional Class II-IV heart failure and an ejection fraction of 35% or less, on ACE inhibitors and diuretics, into one of four trials based on the distance walked in 6 minutes. The Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (PRECISE) study randomized 278 patients with moderate-to-severe heart failure to carvedilol or placebo for 6 to 8 months.[83] Carvedilol had no effect on the primary endpoint of exercise tolerance, but reduced the combined endpoint of death or cardiovascular hospitalizations by 37%. The Multicenter Oral Carvedilol in Heart Failure Assessment (MOCHA) trial randomized 345 patients with moderate-to-severe heart failure to one of three doses of carvedilol (12.5, 25, or 50 mg daily) or placebo.[84] As in PRECISE, treatment with carvedilol had no effect on exercise tolerance but reduced cardiovascular hospitalizations by 45% and all-cause mortality by 73%. The Mild Carvedilol Heart Failure study randomized 366 patients to carvedilol (50 to 100 mg daily) or placebo for up to 12 months.[85] Carvedilol reduced the risk of clinical progression—defined as death, heart failure hospitalization, or an increase in medications—by 48%, and all-cause mortality by 77%. In the severe heart failure study, carvedilol had no effect on the primary endpoint (quality of life), but improved global assessment by physicians and patients and increased ejection fraction.[86]

The U.S. Carvedilol Heart Failure Trials program was stopped prematurely by the Data and Safety Monitoring Board after a median follow-up of only 6.5 months because of a significant mortality benefit of carvedilol compared with placebo (risk reduction, 65%; P <0.0001).[87] Although the survival data were not considered conclusive because of the short follow-up period and small number of deaths (a total of 53), the combined results of the U.S. program led the U.S. Food and Drug Administration to approve carvedilol in 1997 for the treatment of patients with mild-to-moderate heart failure.

Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)

MERIT-HF enrolled 3991 patients with predominantly mild-to-moderate heart failure and an ejection fraction of 40% or less into a randomized placebo-controlled study of sustained release metoprolol (up to 200 mg daily).[88] After a mean follow-up of 1 year, an independent safety committee recommended early termination of the study owing to a 34% lower risk of death in the metoprolol CR/XL group. In addition, metoprolol CR/XL reduced sudden deaths (by 41%), deaths due to worsening heart failure (by 49%), and total hospitalizations, and improved NYHA functional class and quality of life.[89] A post-hoc analysis of MERIT-HF and pooled data from other randomized controlled trials showed that these benefits extend to women, including women with clinically stable severe heart failure.[90]

β-Blocker Evaluation and Survival Trial (BEST)

BEST randomized 2708 patients with moderate-to-severe heart failure to placebo or bucindolol and demonstrated a nonsignificant 10% reduction in total mortality (P = 0.10).[91] Preliminary subgroup analyses suggested that patients with NYHA functional class IV symptoms and black patients tended to have worse outcomes on bucindolol therapy. The lower mortality benefit seen in BEST, when compared with MERIT-HF or CIBIS II, may be related to the population studied, the unique pharmacologic profile of bucindolol, or both.

Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS)

COPERNICUS was designed to test the efficacy of β-blockers in patients with severe heart failure.[92] COPERNICUS randomized 2289 patients with symptoms of heart failure at rest or on minimal exertion, who were clinically euvolemic, and who had an ejection fraction of less than 25%, to carvedilol or placebo. Patients could be enrolled during a heart failure hospitalization, but were excluded from participation if they required intensive care or were receiving intravenous vasoactive therapy. The trial was stopped early (mean follow-up, 10 months) by the Data and Safety Monitoring Board based on the finding of a 35% decrease in the risk of death with carvedilol. In addition, carvedilol decreased the combined risk of death or heart failure hospitalization by 31%.[93] The favorable effects of carvedilol were seen in all subgroups, including the highest-risk patients with recent or recurrent cardiac decompensation or ejection fraction of less than 20%.

Carvedilol and Metoprolol European Trial (COMET)

Given the proven benefits of carvedilol and sustained-release metoprolol relative to placebo, European investigators sought to compare the effects of carvedilol and metoprolol on clinical outcomes in heart failure. COMET randomized 3029 patients with NYHA functional class II-IV heart failure and an ejection fraction of less than 35% to receive carvedilol (target dose 25 mg twice daily) or immediate release metoprolol tartrate (target dose 50 mg twice daily).[94] After a mean follow-up of 58 months, all-cause mortality was 34% for carvedilol and 40% for metoprolol (hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P = 0.0017), with the mortality benefit becoming apparent at about 6 months. Mean maintenance doses of carvedilol and metoprolol were 42 and 85 mg, respectively, with carvedilol exerting slightly greater blood pressure and heart rate lowering effects. The pattern of adverse events usually associated with β-blockade, including bradycardia and hypotension, was similar in the two groups.

Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN)

The beneficial effects of β-blockers on survival after acute myocardial infarction were first shown in low-risk patients before the introduction of ACE inhibitors and thrombolysis. To determine the contemporary role of β-blocker therapy in higher risk patients, CAPRICORN randomly assigned 1959 patients with an ejection fraction of 40% or less within 3 to 21 days after acute myocardial infarction to receive carvedilol

or placebo.[223] Although there was no difference in the primary combined endpoint of death or cardiovascular hospitalization, all-cause mortality was significantly reduced by carvedilol (hazard ratio, 0.77; 95% CI, 0.60-0.98; P = 0.03).

Practical Considerations

Based on the results of controlled clinical trials, it is recommended that all stable patients with current or earlier symptoms of heart failure and reduced ejection fraction should be treated with a β-blocker unless contraindicated or not tolerated. Treatment with a β-blocker should be initiated as soon as left ventricular dysfunction is diagnosed and should not be delayed until the patient fails treatment with other drugs (e.g., ACE inhibitors and diuretics). Patients with minimally symptomatic or asymptomatic left ventricular dysfunction should also receive β-blockers to attenuate ventricular remodeling, to slow disease progression, and to reduce the risk of sudden death. Whether β-blockers are safe and effective in patients with refractory heart failure remains unknown, although data from COPERNICUS suggest that the risk of clinical deterioration may be overstated.[93] In addition, the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial demonstrated that initiation of β-blocker therapy before hospital discharge in stabilized patients is safe, does not increase length of stay, and improves the long-term use of β-blockers.[95]

When beginning therapy with β-blockers, patients should be stable on background therapy consisting of ACE inhibitors and diuretics, with or without digoxin, although they do not need to be taking high doses of ACE inhibitors. There should be no or minimal fluid retention, and patients should not be hospitalized in an intensive care unit or have received positive inotropic therapy for decompensated heart failure. Volume depletion should also be corrected before initiating therapy. β-Blockers are relatively contraindicated in patients with reactive airway disease and in patients with severe bradycardia or conduction system disease that is not treated with a pacemaker. β-Blockers should be used with caution in patients with asymptomatic hypotension (e.g., systolic blood pressure <90 mm Hg). Although there is a theoretical concern that β-blockers may mask signs of hypoglycemia in the setting of diabetes, diabetic patients were not excluded from clinical trials. Furthermore, carvedilol was shown to have favorable metabolic effects and may delay the progression to microalbuminuria in patients with type 2 diabetes mellitus and hypertension.[96]

β-Blockers should be initiated at very low doses (e.g., bisoprolol 1.25 mg once daily, carvedilol 3.125 mg twice daily, metoprolol XL 12.5 to 25 mg once daily) and titrated slowly over several weeks as tolerated (see Table 14–5). During the titration phase, patients should be monitored closely for the development of adverse drug effects, including hypotension, worsening heart failure, or bradycardia. Family members should also be educated about potential side effects and how to monitor for drug intolerance. Hypotension is the most common side effect associated with β-blockers, especially with agents with concomitant α_1-blockade (e.g., carvedilol) and in the setting of volume depletion. Typically, patients describe mild lightheadedness, dizziness, or blurred vision, which resolves after a few doses, but syncope may occur. Strategies for managing hypotensive symptoms include taking β-blockers with food to slow absorption, staggering or reducing the doses of other vasodilators (e.g., ACE inhibitors), or reducing diuretic therapy. If symptoms persist, the dose of β-blocker should be decreased; abrupt withdrawal should be avoided.

Because the failing heart is dependent on adrenergic support, clinical heart failure status may worsen during the initiation of β-blocker therapy.[97] Although fluid retention and fatigue are less common than symptoms associated with hypotension, they are more likely to lead to β-blocker withdrawal.[87] Fluid retention, which may manifest as pulmonary and systemic venous congestion, can usually be managed with an increase in oral diuretics, whereas fatigue may require a decrease in the β-blocker dose. The management of acute decompensated heart failure in the setting of β-blocker initiation is discussed in Chapter 17. Another cause for hypotension or fatigue in patients recently started on β-blockers is bradycardia or heart block. Initial management includes assessing for laboratory or electrocardiographic evidence of digoxin toxicity and lowering the dose of β-blocker. If other medications with negative chronotropic effects are contributing (e.g., amiodarone, antidepressants), they should be stopped or permanent pacing should be considered. The role of right ventricular or biventricular pacing to allow for β-blockade, especially in mildly symptomatic or asymptomatic patients, is unknown.

Given the possibility of adverse effects occurring during initiation of β-blockers, upward titration should not occur until the patient is stable on the current dose. Overall, 10% to 15% of patients will not tolerate long-term therapy with β-blockers, although this rate may be higher in patients with more advanced disease[86] and in the elderly.[98] The optimal dosing of β-blockers in patients with heart failure is not known. In the MOCHA trial, in which patients were randomized to three different doses of carvedilol, there were trends toward a dose-dependent increase in ejection fraction and a decrease in mortality rates.[84] However, even patients randomized to low-dose carvedilol received significant clinical benefits. Similar clinical efficacy of low-dose versus high-dose metoprolol CR/XL was seen in MERIT-HF.[99] Therefore, although an attempt should be made to titrate β-blockers to the target doses used in controlled clinical trials (see Table 14–5), low-dose β-blocker therapy is preferred to no therapy. Patients should be advised that the clinical benefits of β-blockers may not become apparent for weeks to months, that they may feel worse before they feel better, and that the primary goals of therapy are to slow disease progression and prolong survival.

Choice of β-Blocker

Three β-blockers prolong survival and are approved by the U.S. Food and Drug Administration for the treatment of heart failure: bisoprolol, sustained-release metoprolol, and carvedilol. Nebivolol prolonged the time to death or hospitalization in elderly heart failure subjects,[98] but is not available in the United States. There are no controlled data on the use of atenolol in heart failure. Although some remodeling[100] and survival data[94] suggest that carvedilol is superior to metoprolol, these studies were flawed by the use of immediate-release metoprolol at a lower β_1-blocking dose. No studies have directly compared sustained-release metoprolol with

carvedilol at target doses, but review of the COPERNICUS and MERIT-HF studies suggests a similar reduction in all-cause mortality and sudden death. Metoprolol CR/XL may be preferred in patients with reactive airway disease or in whom compliance or cost is an issue. Carvedilol may be more effective at lowering blood pressure in hypertensive patients and improving insulin sensitivity in diabetics.[96] Carvedilol has also been shown to be safe and effective in stable patients with severe heart failure.[92]

OPTIONS FOR PATIENTS WHO REMAIN SYMPTOMATIC DESPITE STANDARD THERAPY

Patients who have persistent signs and symptoms of heart failure despite intensive treatment with diuretics, ACE inhibitors or angiotensin receptor blockers, and β-blockers present a difficult challenge for physicians who are treating patients with heart failure. Several pharmacologic, device, and surgical options are currently available and may require consultation with a heart failure specialist to optimize therapy for the individual patient. For patients with symptomatic heart failure, aldosterone antagonists and digoxin should be considered as adjunctive therapy to reduce the rates of morbidity and mortality that are related to progressive left ventricular failure. The combination of hydralazine and isosorbide dinitrate is indicated in black patients with moderate-to-severe heart failure and reduced ejection fraction. For patients with advanced or refractory heart failure, there are several options that can be considered individually or in combination (Table 14–9). Some patients will require multiple diuretics (e.g., loop and thiazide diuretics) or multiple vasoactive agents (e.g., combination of ACE inhibitors, angiotensin receptor blockers, and/or isosorbide dinitrate). A small number of selected patients may be candidates for ultrafiltration, mechanical circulatory support, and/or cardiac transplantation (see Chapter 18 and Appendix 3).

Cardiac resynchronization therapy improves contractile performance acutely in patients with dilated cardiomyopathy and intraventricular conduction delay and reduces the rates of morbidity and mortality in chronic heart failure (see Chapter 15). High-risk coronary artery bypass grafting and newer cardiac surgical procedures such as left ventricular reconstructive surgery and mitral valvuloplasty may reduce wall stress and cause reverse ventricular remodeling in patients with ischemic or nonischemic cardiomyopathy (see Chapter 16). However, these procedures have not been shown to prolong survival compared with medical therapy[101] and are limited to specialized centers. Continuous infusions of positive inotropic agents may be used as palliative care to bridge patients to end of life, or in selected patients as a bridge to cardiac transplantation. The subsequent discussion will focus on adjunctive pharmacologic therapy.

DIGOXIN

Pharmacologic and Clinical Effects

The mechanisms of action and the pharmacology of digoxin are discussed in Chapter 23 in HD7e and in other reviews.[102,103] Through its inhibition of sodium-potassium adenosine triphosphatase, digoxin affects cellular processes in the heart (increased cardiac contractility), vagal afferents (decreased sympathetic outflow), and kidney (decreased renin secretion) that contribute to its cardiovascular effects. Although digoxin has been commonly used in the management of heart failure, there was considerable controversy regarding the precise documentation of its clinical efficacy. Early studies were conflicting and interpretation was difficult because of small sample sizes and dependence on less precise clinical measures. Data from larger and more conclusive randomized controlled trials[104-108] have provided the scientific data to recommend the use of digoxin to decrease hospitalizations for heart failure in patients with reduced ejection fraction and current or earlier symptoms of heart failure.[4]

Many of the early trials that evaluated the efficacy of digoxin used a crossover design and sample sizes that are considered small in comparison with later multicenter trials. Subsequent trials used a parallel design in which digoxin was compared with placebo and other inotropic and/or vasodilator agents, including xamoterol, captopril, milrinone, and ibopamine. The German and Austrian Xamoterol Study Group randomized 433 patients to either placebo, digoxin, or xamoterol, a mixed β-agonist with some β-blocker activity.[104] Digoxin and xamoterol decreased symptoms of heart failure compared with placebo. The Captopril Digoxin Multicenter Research group randomized 300 patients to either placebo, digoxin, or captopril.[105] At 6 months, digoxin increased ejection fraction and reduced hospitalizations for heart failure, whereas captopril improved exercise duration and NYHA functional class. In other trials comparing digoxin with oral inotropic therapy, digoxin decreased neurohormonal activation and markedly decreased the frequency of clinical decompensation.[106,107] Two trials examined the effect of withdrawal

Table 14–9 Therapeutic Options for Patients with Advanced or Refractory Heart Failure

Approved	Investigational
Combination diuretics	Vasopressin receptor antagonists
Additional vasodilators	Adenosine receptor antagonists
Positive inotropic agents	Phosphodiesterase type 5 inhibitors
Cardiac resynchronization therapy	Intermittent natriuretic peptide infusions
Mechanical circulatory support	Erythropoietic agents
Cardiac transplantation	Enhanced external counterpulsation
Left ventricular reconstructive surgery	Implantable hemodynamic monitor
Surgical mitral valvuloplasty	Percutaneous mitral valvuloplasty
Intrathoracic impedance monitor	

of digoxin in heart failure patients who were treated with a diuretic only,[109] or with a diuretic and an ACE inhibitor.[110] In both trials, the withdrawal of digoxin resulted in a decrease in exercise tolerance, worsening heart failure symptoms, and lower ejection fraction.

Although these studies demonstrated the beneficial effects of digoxin on clinical endpoints, virtually all of these trials were unable to assess an effect on survival because of inadequate sample size. In addition, retrospective data in patients after acute myocardial infarction suggested that digoxin increased mortality.[111] The effect of digoxin on mortality in patients with chronic heart failure was assessed in the Digitalis Investigation Group (DIG) trial.[108] In the DIG trial, 6800 patients with mild-to-moderate heart failure and an ejection fraction of 45% or less were randomized to digoxin or placebo in addition to diuretics and ACE inhibitors. After a mean follow-up of 37 months, there were 1181 deaths in the digoxin group and 1194 deaths in the placebo group (risk reduction, 0.99; $P = 0.80$). Digoxin reduced the risk of death or hospitalization due to worsening heart failure, but tended to increase the risk of death due to other causes.

The cumulative data from controlled trials suggest that digoxin is associated with important clinical improvements without adverse effects on survival. Furthermore, these benefits have been seen in a wide range of patients, regardless of the cause of heart failure, the underlying rhythm, or concomitant medical therapy. The results of the DIG trial led the U.S. Food and Drug Administration to approve digoxin for the treatment of heart failure in 1997. According to revised ACC/AHA guidelines, the goals of digoxin therapy should be to alleviate symptoms and improve clinical status in patients with heart failure who are being treated with diuretics, an ACE inhibitor, or angiotensin receptor blocker, and a β-blocker. Digoxin has not been shown to be effective in patients with heart failure and preserved systolic function and may have adverse effects in patients with acute coronary syndromes. There are no data to support the use of digoxin in patients with asymptomatic left ventricular dysfunction.

Practical Considerations

Previous practice typically involved the use of full digitalizing doses to more rapidly achieve therapeutic levels. However, this is no longer recommended, and patients should simply be started on maintenance doses ranging from 0.0625 to 0.25 mg per day. Steady-state levels will be reached in approximately 1 week. Because drug elimination is primarily via the kidneys, digoxin doses must be adjusted in patients with acute or chronic kidney disease. There are a number of drug interactions that can significantly influence the efficacy and toxicity of digoxin.[103] Drugs known to increase digoxin levels include verapamil, spironolactone, and amiodarone. It is common practice to empirically reduce digoxin doses when initiating therapy with these drugs with close follow-up of digoxin levels. In addition, lower doses are recommended in elderly patients with heart failure.[112] Digoxin is not indicated to stabilize patients with acute decompensated heart failure (see Chapter 17) and should be used with caution in patients with post-myocardial infarction ischemia.

There is little evidence to support the routine use of serum digoxin levels to guide dose selection. However, it is reasonable to check a digoxin level during follow-up to identify patients who are receiving subtherapeutic doses, which in some cases is secondary to noncompliance. Digoxin levels are also extremely important in the evaluation of toxicity, such as in patients who develop nausea, anorexia, arrhythmias, atrioventricular block, or confusion. Digoxin toxicity is usually associated with serum levels of more than 2.0 ng/mL, but can occur with lower serum levels in the setting of hypokalemia or hypomagnesemia. Retrospective analyses from the DIG trial also suggest that serum digoxin concentrations in the "high-normal" range (e.g., 1.2 to 2.0 ng/mL) are associated with an increased risk of death for both men and women.[113,114] Taken together, these data suggest that the efficacy and safety of digoxin can be optimized by using doses that achieve a serum level in the range of 0.5 to 1.0 ng/mL. Of note, this recommendation has not yet been incorporated into reference ranges provided by clinical laboratories.

For many years, digoxin has been used to control the ventricular response rate in atrial fibrillation. In many situations, however, digoxin may not provide adequate rate control, especially during exercise, in patients with high sympathetic tone, or in the elderly. In patients with heart failure and atrial fibrillation already receiving a β-blocker, digoxin may be used as adjunctive therapy to control ventricular rate. Alternatively, amiodarone may be safely used for both ventricular rate control and restoration and maintenance of normal sinus rhythm.[115] In patients with symptomatic atrial fibrillation who do not respond to or who are intolerant of anti-arrhythmic therapy, options include atrioventricular junction ablation with back-up pacing or pulmonary vein isolation using radiofrequency or surgical ablation (see Chapters 20 and 24).

ALDOSTERONE ANTAGONISTS

Pathophysiology

In addition to systemic vasoconstriction and intravascular volume expansion, renal release of angiotensin in heart failure also results in increased levels of aldosterone, which is known to play an important role in the pathophysiology of heart failure.[116] Aldosterone promotes sodium retention, sympathetic activation, and baroreceptor dysfunction, and causes myocardial and vascular fibrosis. Although ACE inhibitors decrease aldosterone levels acutely, chronic ACE inhibition is associated with unsustained aldosterone suppression, referred to as "aldosterone escape."[117] Spironolactone competitively inhibits aldosterone-sensitive sodium channels in the cortical collecting tubule of the kidney and causes sodium and free-water excretion and potassium retention. Similar to the antiremodeling effects of ACE inhibitors and angiotensin receptor blockers, spironolactone inhibits aldosterone receptors in the heart and systemic vasculature that mediate pleiotropic effects leading to ventricular and vascular remodeling. In animal and human studies, spironolactone has been shown to prevent myocardial hypertrophy and fibrosis and to improve vascular compliance.

Clinical Efficacy

In the past, spironolactone was used infrequently as a potassium-retaining diuretic in patients with advanced heart failure, refractory edema, and hypokalemia. With the recognition of

"aldosterone" escape in heart failure and pilot studies demonstrating the safety of adding spironolactone to an ACE inhibitor,[118] a large mortality study of aldosterone antagonism was carried out. The Randomized Aldactone Evaluation Study (RALES) randomly assigned 1663 patients with severe heart failure and an ejection fraction of 35% or less to treatment with spironolactone (25 mg daily) or placebo.[119] The trial was stopped early after a mean follow-up of 24 months because of a 30% reduction in all-cause mortality rates with spironolactone. In addition, spironolactone improved symptoms and reduced the need for hospitalization owing to heart failure. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the addition of aldosterone antagonists to optimal medical therapy reduced morbidity and mortality rates among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.[120] A multicenter randomized controlled trial is currently testing the effects of spironolactone on the morbidity and mortality rates in patients with heart failure and preserved systolic function.

Practical Considerations

Adjunctive therapy with aldosterone antagonists should be considered in selected patients with advanced heart failure or with post-myocardial infarction left ventricular dysfunction. The major risk associated with aldosterone blockade is hyperkalemia, which, in some cases, may be exacerbated by worsening renal function. Although the incidence of serious hyperkalemia was minimal in the RALES trial (1% placebo, 2% spironolactone; $P = 0.42$), it is important to note that patients were not enrolled if serum creatinine exceeded 2.5 mg/dL. In addition, potassium supplements were discontinued and electrolytes and renal function were monitored closely. After publication of these results, the rates of spironolactone prescriptions, hospitalization for hyperkalemia, and the associated mortality rate increased significantly.[121] Use of aldosterone antagonists in a broader patient population (e.g., the elderly, patients with chronic kidney disease, patients with heart failure with preserved ejection fraction)[122] and less rigorous monitoring of serum potassium levels[123] may explain these higher complication rates. Antiandrogenic effects, which may also limit the use of spironolactone, include painful gynecomastia, impotence, and menstrual irregularities (see Table 14–7). These hormonal effects are generally not seen with the selective aldosterone antagonist eplerenone.

Spironolactone should be initiated at a dose of 12.5 mg once daily and eplerenone at a dose of 25 mg per day. Potassium supplementation should be decreased or discontinued, and follow-up laboratory studies should be checked within 1 week. Patients should be counseled on avoiding foods (e.g., bananas, avocados, and broccoli) and salt substitutes that may contain high quantities of potassium. In addition, medications that can aggravate renal dysfunction, such as nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, should be avoided. Any change in cardiac medications that may affect renal function or volume status, such as ACE inhibitor titration or use of combination diuretics, requires reassessment of serum electrolytes and renal function. Depending on the severity of hyperkalemia, treatment may include permanent discontinuation of the aldosterone antagonist, temporary discontinuation of other renin angiotensin system inhibitors and potassium supplements, and use of exchange resins.

HYDRALAZINE AND ISOSORBIDE DINITRATE

The combination of hydralazine and isosorbide dinitrate was shown in V-HeFT I to be an efficacious combination in terms of an improvement in survival compared with placebo.[40] Moreover, in V-HeFT II, this combination tended to increase exercise capacity and ejection fraction more than did enalapril.[41] Experience from these two large trials clearly demonstrated the usefulness and benefits of this drug combination. Retrospective analysis of the V-HeFT studies suggested particular efficacy in blacks.[124] To test whether this combination provides additional benefit in this specialized population, the African American Heart Failure Trial (A-HeFT) randomized 1050 self-identified blacks with NYHA functional class III-IV heart failure and dilated ventricles to receive a fixed dose of isosorbide dinitrate plus hydralazine (target daily doses of 120 mg and 225 mg, respectively) or placebo in addition to standard therapy.[125] The study was stopped early owing to a significantly higher mortality rate in the placebo group than in the group given isosorbide dinitrate plus hydralazine (10.2% versus 6.2%; P=0.02). Combination therapy also reduced the rate of heart failure hospitalizations by 33% and improved quality of life.

Although originally believed to be effective as vasodilators, emerging evidence suggests that the benefits of hydralazine and isosorbide dinitrate are related more to their biologic effects. For example, nitrates may attenuate myocardial and vascular remodeling by increasing the bioavailability of nitric oxide,[126] and hydralazine has been shown to prevent nitrate tolerance through antioxidant activity.[127] Hydralazine attenuates nitrate tolerance through inhibition of NADH/NADPH oxidases as well as through direct scavenging of reactive oxygen species (see Chapter 5). By favorably altering the nitroso-redox balance in heart failure,[126] the combination of nitrates and hydralazine may prevent myocardial hypertrophy, fibrosis, and apoptosis and may improve vascular compliance. Although these mechanisms have not been explored directly in randomized controlled trials, preliminary data from the A-HeFT study demonstrates clinical benefits independent of baseline blood pressure as well as reverse ventricular remodeling. It is also not known whether these mechanisms of benefit are of greater importance for blacks than for other racial or ethnic groups. Preliminary studies demonstrate impaired flow-mediated vasodilation in black hypertensive patients compared with whites but are limited by small numbers and potential confounders.[128] Others have shown a more generalized abnormality in endothelium-dependent vasodilation in heart failure,[129] which could be favorably affected by nitric oxide-enhancing therapy. Additional studies to understand the genetic and environmental determinants of the effect of hydralazine and nitrates on disease progression in heart failure are currently underway.

Practical Considerations

A number of factors have limited the widespread application of hydralazine-isosorbide dinitrate to patients with heart

failure. First, in V-HeFT II, the ACE inhibitor enalapril resulted in a significant improvement in survival compared with hydralazine and isosorbide dinitrate. Second, this combination is considerably more cumbersome for patient compliance because the target doses used in the V-HeFT studies were 160 mg of isosorbide dinitrate (40 mg four times daily) and 300 mg of hydralazine (75 mg four times daily). Although a fixed combination pill that can be taken three times daily is now available, compliance and cost remain problematic for patients already taking several heart failure medications. Third, this combination has a number of side effects, including headaches and flushing associated with nitrate preparations and gastrointestinal symptoms from hydralazine. In the V-HeFT trials, between 18% and 38% of patients discontinued one or both of the medications owing to side effects. In A-HeFT, adverse effects of isosorbide dinitrate-hydralazine included headache (50%), dizziness (32%), and nausea (10%) with one in five patients discontinuing the fixed-dose combination.

In clinical practice, the combination of hydralazine and isosorbide dinitrate may be particularly useful in patients who have persistent symptoms of heart failure, but are unable to tolerate renin-angiotensin system inhibitors. However, there have been no studies specifically targeting this patient population, and hydralazine and nitrates should not be substituted for ACE inhibitors or angiotensin receptor blockers. Many physicians use nitrates in their patients with heart failure, especially those with underlying ischemic heart disease.[130] Based on both mechanistic and trial data, it would be prudent to administer nitrates in combination with hydralazine. Furthermore, revised ACC/AHA guidelines recommend the addition of a combination of hydralazine and a nitrate for patients with reduced ejection fraction who are already taking an ACE inhibitor and β-blocker and who have persistent symptoms.

The most important recommendation regarding this regimen is to initiate therapy with low doses followed by gradual dose titration over several weeks. Initial doses of more than 10 mg isosorbide dinitrate and 25 mg hydralazine may produce headaches, but gradual upward titration is usually well tolerated. Prophylactic acetaminophen can reduce the problems associated with nitrate-induced headache, whereas nonsteroidal anti-inflammatory agents should be avoided. Several long-acting nitrate preparations are available, but the clinical experience with these formulations in patients with heart failure is limited.

CALCIUM CHANNEL BLOCKERS

Calcium channel blocking agents have been considered for use in patients with heart failure because these drugs have potent vasodilator actions and may reduce ischemia in patients with left ventricular dysfunction due to coronary artery disease.[131] Hemodynamic studies have demonstrated that acute administration of calcium channel blockers is associated with a reduction in systemic vascular resistance and an increase in cardiac output. However, the acute hemodynamic effects of nifedipine, verapamil, and diltiazem have not been uniform, and short- and long-term treatment with these agents has been associated with serious adverse events and excess mortality, possibly related to negative inotropic effects or neurohormonal stimulation.

Second-generation calcium channel blockers with greater selectivity for vascular actions have also been evaluated in heart failure. Amlodipine, a long-acting dihydropyridine with potent vasodilator effects, is approved for the treatment of hypertension and angina. In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study, 1153 patients with severe heart failure and an ejection fraction of less than 30% were randomized to amlodipine (up to 10 mg daily) or placebo for 6 to 33 months.[132] Amlodipine had no effect on the primary combined endpoint of death or major cardiovascular hospitalization, but tended to reduce all-cause mortality (risk reduction, 16%; $P = 0.07$), particularly in nonischemic cardiomyopathy. However, PRAISE II demonstrated no beneficial effects of amlodipine on neurohormonal stimulation or survival in this population.[133] Similar negative findings were seen in the V-HeFT III study in which long-term therapy with felodipine had no beneficial effects on exercise tolerance, hospitalizations, or survival, and was associated with a higher incidence of peripheral edema.[134] Finally, data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggest that the antihypertensive benefits of amlodipine may be offset by an increased risk of developing heart failure.[135]

Based on these cumulative data, it is recommended that most calcium channel blockers should be avoided in patients with heart failure. The primary benefit may be mainly from control of hypertension or reduction of ischemia, although alternative agents (e.g., nitrates) or treatments (e.g., revascularization) are preferred. Of the available calcium channel blockers, only the vasoselective agents have not been shown to adversely affect survival in patients with heart failure and reduced ejection fraction. Calcium channel blockers may have a role in controlling heart rate or improving symptoms in patients with heart failure and preserved ejection fraction (see later).

POSITIVE INOTROPIC AGENTS

Oral Positive Inotropes

The search for safe and effective inotropic agents for patients with heart failure was based on the observation that the clinical syndrome of heart failure results from a primary defect in myocardial contractility and that many patients have symptoms that are refractory to standard therapy. During the 1980s and early 1990s, there was an extraordinary effort to develop an orally administered inotropic agent.[136] The majority of studies focused on phosphodiesterase (PDE) inhibitors, which produce a marked hemodynamic benefit when administered acutely to patients with decompensated heart failure. However, enthusiasm for this class of drugs decreased significantly when multicenter trials failed to detect a significant improvement in symptoms and exercise tolerance[137] and when the PROMISE (Prospective Randomized Milrinone Survival Evaluation) trial demonstrated increased mortality rates in patients treated with milrinone.[138] Other oral inotropes with PDE inhibitor effects have also been associated with excess mortality in heart failure, including vesnarinone[139] and high-dose enoximone.[140] Studies of low-dose enoximone have yielded disappointing clinical results (although neutral effects on mortality) in patients with advanced heart failure.[141]

Intravenous Positive Inotropes

An additional treatment that can be considered in patients with refractory heart failure is intravenous dobutamine or milrinone.[142] Dobutamine augments cardiac contractility primarily via stimulation of β-adrenergic receptors and is a modest vasodilator, whereas milrinone exerts potent inotropic and direct vasodilator effects via PDE inhibition in the myocardium and vasculature (see Chapter 17 for discussion of pharmacology and short-term use of inotropic therapy in acute decompensated heart failure). A small number of patients with end-stage heart failure cannot be weaned from acute inotropic therapy. Evidence of failure to wean includes the development of symptomatic hypotension, recurrent congestion, and/or worsening renal function. In practice, more than one attempt should be made to wean inotropes, and weaning should not be undertaken until the patient has achieved clinical stability. In addition, ACE inhibitors and β-blockers may need to be held for increased blood pressure and renal perfusion. Invasive monitoring for "optimization" of hemodynamics is not required or recommended.[143] For selected patients deemed to be inotrope dependent, chronic intravenous therapy may be used as a bridge to transplant or to the end of life.

Bridge to Transplant

Because of the limited donor supply, the majority of patients receiving heart transplants require pharmacologic or mechanical cardiac support as a bridge to transplant (see Chapter 18). Options for inotrope-dependent patients include in-hospital or continuous home intravenous therapy. Criteria for discharge to home include hemodynamic stability on low-dose of a single agent, improved functional status, and family and nursing support. Implantable cardioverter-defibrillators (ICDs) are recommended to prevent sudden death. Home dobutamine and milrinone have been used successfully to bridge patients to transplant, although readmissions and complications are common. In one study, 59% of patients required readmission: two thirds of readmissions due to worsening heart failure and one third due to infection or occlusion of the indwelling catheter.[144]

Bridge to End of Life

For patients with refractory heart failure who are not transplant candidates, chronic inotropic therapy may be used to palliate symptoms at the end of life. This practice has become more common as cardiologists care for older patients who have exhausted medical and surgical options, and for whom the use of β-blockers and ICDs has decreased the risk of sudden death in favor of progressive pump failure. Hershberger and colleagues[142] reported a 10-year experience with home inotropic infusions in nontransplant patients with end-stage heart failure. Although patients were ambulatory and pain free at the time of discharge, the median survival was only 3 months, and one-third of patients died in the hospital. In practice, palliative inotropic therapy requires collaboration with home hospice to facilitate coadministration of narcotics and anxiolytics and requires a discussion with the patient and family about turning off ICDs.

Inotropic agents have also been administered intermittently at home or in an infusion clinic. Although initial uncontrolled studies suggested improvement in symptoms and decreased hospitalizations, small randomized studies have demonstrated either no benefit or excess mortality.[145] The primary mechanism responsible for increased mortality associated with chronic inotropic infusions is believed to be an increase in intracellular cyclic AMP, which exerts a direct toxic effect on the myocardium leading to further contractile dysfunction and proarrhythmia.[146] Hypersensitivity myocarditis with dobutamine may also contribute to hemodynamic deterioration.[147] Because of the lack of data demonstrating efficacy and the concerns about toxicity, the use of intermittent inotropic infusions is not recommended for the treatment of advanced heart failure.[4]

ANTITHROMBOTIC THERAPY

Many clinicians have recommended anticoagulation for prophylaxis against thromboembolism and stroke for patients with dilated cardiomyopathy in the absence of specific contraindications.[148] This recommendation is based on the presence of ventricular thrombus in as many as 75% of cases of dilated cardiomyopathy[149] and on the repeated observation of a high incidence of embolic events in this patient population.[150,151] In addition, retrospective analyses have suggested that the incidence of embolic events[152] and all-cause mortality[153] is reduced in patients who are treated with anticoagulants. The mechanisms underlying the increased risk of thromboembolism in patients with heart failure include stasis of blood in the cardiac chambers and systemic venous circulation and hypercoagulability. Additionally, patients with heart failure are at increased risk for the development of atrial fibrillation,[154] which predisposes to cardiac thrombi formation.

Recommendations for the routine use of anticoagulants in patients with heart failure have been reconsidered in view of data from multicenter trials. In V-HeFT II, there were only 46 embolic events in 804 patients followed for an average of 2.5 years.[155] Furthermore, V-HeFT II demonstrated an *increased* thromboembolic rate in patients receiving anticoagulation compared with those not receiving anticoagulation (4.9 versus 2.1 per 100 patient years, $P = 0.01$). In SOLVD, the annual incidence of thromboembolic events was only 2.4% in women and 1.8% in men. The use of anticoagulants, as directed by individual physicians, was not associated with a reduced incidence of thromboembolism.[156] Unfortunately, randomized controlled trials of anticoagulation in heart failure have been inconclusive owing to small sample size[69] or have been prematurely stopped owing to lack of enrollment.[68]

Because the risk of thromboembolism and the benefits of anticoagulants may not be as large as once considered, and in the absence of data from controlled trials,[157] recommendations for anticoagulation for patients with heart failure should be made on an individual basis. Indications for anticoagulation are atrial fibrillation and a history of thromboembolism. Consideration of anticoagulation should also be given to patients with intracavitary thrombus or spontaneous contrast demonstrated by echocardiography, or with specific diagnoses associated with a higher thromboembolic risk such as cardiac amyloidosis, left ventricular noncompaction, and peripartum cardiomyopathy. Younger patients with familial dilated cardiomyopathy and a family history of thromboembolism should also be considered for anticoagulation. In patients with

contraindications to warfarin, an alternate regimen is to use a single daily dose of aspirin, but there are no controlled data to support this recommendation. In addition, as discussed, aspirin may attenuate the benefits of ACE inhibition in heart failure and is not recommended for patients with nonischemic cardiomyopathy.

ANTIARRHYTHMIC THERAPY

The indications for and the efficacy of antiarrhythmic agents in the management of heart failure remain subjects of great controversy.[158] The original rationale for considering these agents as adjunctive therapy was based on the observation that as many as 30% to 50% of all deaths in patients with heart failure can be classified as sudden death. Frequent ventricular premature contractions and nonsustained ventricular tachycardia on Holter recordings are almost universal in patients with heart failure and are frequent sources of concern in hospitalized patients who are on telemetry monitoring. These arrhythmias are likely related to a number of factors, including fibrosis, wall stress, left ventricular dilatation, electrolyte imbalances, high levels of circulating catecholamines, and proarrhythmic effects of drugs such as digoxin. All of these factors suggested that antiarrhythmic therapy and suppression of high-risk arrhythmias might be beneficial in this patient population. However, the understanding that sudden death in heart failure may be caused by ischemia or bradyarrhythmias,[159] and the increased recognition of adverse events associated with antiarrhythmic therapy including proarrhythmia, worsening heart failure,[160] and excess mortality rate as shown in controlled trials[161] led to the recommendation to avoid the use of class I antiarrhythmic drugs.

Subsequent studies focused on the role of class III agents (e.g., amiodarone, d-sotalol, and dofetilide) in heart failure. Amiodarone may substantially reduce the frequency and complexity of asymptomatic ventricular arrhythmias, and initial studies suggested that amiodarone may have a beneficial impact on morbidity and mortality rates in patients with heart failure.[162] The Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy (CHF-STAT) was a prospective, double-blind study in which 674 patients with heart failure, an ejection fraction of 40% or less, and asymptomatic ventricular ectopy were randomized to amiodarone or placebo for a median of 45 months.[163] As expected, amiodarone decreased ventricular ectopy compared with placebo. In contrast to a smaller, unblinded study, CHF-STAT demonstrated no beneficial effect of amiodarone on mortality. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) also showed no effect of amiodarone on survival in a study of more than 2500 patients with ischemic and nonischemic cardiomyopathy.[164]

Although amiodarone has no role in the treatment of heart failure per se, it may be useful in the management of symptomatic ventricular or atrial arrhythmias that complicate heart failure. In particular, amiodarone may be administered acutely to control ventricular response in heart failure patients with atrial fibrillation, and its long-term use may restore and maintain sinus rhythm.[115,165] Amiodarone may also be used to suppress symptomatic ventricular tachycardia, especially in patients who are receiving frequent ICD shocks. Close monitoring for adverse reactions, including hepatic, pulmonary and thyroid toxicity, and knowledge of drug interactions such as increased digoxin levels and elevated INR are critical to the safe use of amiodarone. In contrast to type I agents, amiodarone appears to be associated with a very low risk of proarrhythmia in patients with left ventricular dysfunction.[166]

Other class III antiarrhythmic agents that have been tested in heart failure are the potassium-channel blocker, d-sotalol, and dofetilide. In the Survival With Oral d-sotalol (SWORD) trial, 3121 patients with ischemic cardiomyopathy were randomized to treatment with d-sotalol (200 mg twice daily) or placebo.[167] The trial was stopped early because of the excess mortality rate in the d-sotalol group, which appeared to be primarily arrhythmic. The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) study group demonstrated no effect of dofetilide on the mortality rate in 1518 patients with symptomatic left ventricular dysfunction.[168] Like amiodarone, dofetilide was effective in converting atrial fibrillation to sinus rhythm; however, it was associated with a 3.3% incidence of torsades de pointes. The role of ICDs for primary and secondary prevention of sudden death in heart failure is discussed in Chapter 15.

SPECIAL CONSIDERATIONS

The majority of ambulatory patients with heart failure and reduced ejection fraction can be treated with medications according to the recommendations presented in this chapter. There are, however, several subgroups of patients who merit special consideration because other pharmacologic therapy may provide important clinical benefit.

Patients with Heart Failure and Normal Ejection Fraction

As many as one half of patients presenting with heart failure have a normal or near normal left ventricular ejection fraction.[169] Heart failure with preserved systolic function is relatively uncommon in young or middle-aged adults, yet the prevalence can exceed 50% in older patients, especially elderly women with hypertension.[170] In addition to hypertensive heart disease, other causes of heart failure with normal ejection fraction are restrictive, hypertrophic and infiltrative cardiomyopathies, and constrictive pericarditis. Diastolic dysfunction is believed to be the primary mechanism responsible for this clinical syndrome, but other pathophysiologic factors may contribute to disease progression, including arterial stiffness, sodium avidity, and renal dysfunction. Some data suggest that long-term survival is similar among patients with reduced versus preserved systolic function,[171] but most studies show that heart failure with normal ejection fraction is associated with a lower risk of death (Table 14–10).[172]

Large randomized trials have confirmed survival and other benefits of ACE inhibitors and β-blockers in patients with heart failure and reduced ejection fraction, yet there have been few such trials in patients with preserved systolic function. As a result, therapy is based primarily on the results of clinical investigations in small groups of patients, and on pathophysiological concepts.[173] Principles of therapy include blood pressure and heart rate control, reduction in cardiac filling pressures, and prevention of myocardial ischemia (Table

Table 14–10 Mortality in Heart Failure with Reduced versus Preserved Ejection Fraction

Study	Patients, *N*	Follow-Up	Mortality with Reduced EF	Mortality with Preserved EF	RR of Death with Preserved EF
Cohn 1990[224]	623	2.3 years	19% per year	8% per year	0.42
Ghali 1992[225]	78	2 years	46%	26%	0.56
McDermott 1997[226]	192	27 months	35%	35%	0.97
Vasan 1999[227]	73	5 years	64%	32%	0.50
McAlister 1999[228]	566	3 years	38%	34%	NA
Philbin 2000[229]	1291	6 months	18%	15%	0.69
Masoudi 2003[230]	413	6 months	21%	13%	0.49

EF, ejection fraction; NA, not available; RR, relative risk.

Table 14–11 ACC/AHA Recommendations for Management of Heart Failure with Preserved Ejection Fraction

Class	Recommendation	Level of Evidence
I	Control systolic and diastolic hypertension	A
	Control ventricular rate in atrial fibrillation	C
	Diuretics to control pulmonary congestion and peripheral edema	C
IIa	Coronary revascularization if ischemia is having an adverse effect on cardiac function	C
IIb	Restoration of sinus rhythm if atrial fibrillation is present	C
	β-Blockers, ACE inhibitors, ARBs, or calcium channel blockers to minimize symptoms of heart failure	C
	Digoxin to minimize symptoms of heart failure	C

ACC, American College of Cardiology; AHA, American Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. Adapted from Hunt SA, Abraham WT, Chin MH, et al: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. Circulation 2005;112:e154-e235.

14–11). In heart failure due to hypertension, blood pressure control is important to prevent progression of left ventricular hypertrophy and possibly to promote its regression. In addition, effective antihypertensive therapy may improve diastolic filling properties, relieve the load on the left atrium, and help preserve sinus rhythm.

Calcium channel blockers may reduce symptoms of diastolic heart failure not only by lowering blood pressure, but also by improving ventricular relaxation.[174] Renin-angiotensin system inhibitors (e.g., ACE inhibitors and angiotensin receptor blockers) may also improve ventricular relaxation, slow or reverse myocardial fibrosis, and prevent atrial fibrillation.[175] There is, however, no evidence that either calcium channel blockers or ACE inhibitors improve survival in patients with heart failure and normal ejection fraction. The effect of angiotensin receptor blockers on morbidity and mortality rates was tested in the CHARM-Preserved study. In CHARM-Preserved, 3023 patients with NYHA functional class II-IV heart failure and an ejection fraction greater than 40% were randomized to receive candesartan (target dose 32 mg once daily) or placebo and followed for a median of 36 months.[217] Candesartan had no significant effect on the primary combined endpoint of cardiovascular death or heart failure hospitalization (hazard ratio 0.89; 95% CI, 0.77 to 1.03; $P = 0.12$), but it did reduce the number of patients admitted once or multiple times for heart failure and decreased the risk of diabetes. Adverse events, including hypotension, renal insufficiency, and hyperkalemia, were more common with candesartan. Ongoing multicenter studies will help to further define the risk-benefit profile of renin-angiotensin-aldosterone system inhibitors in patients with heart failure and preserved systolic function (Table 14–12).

Patients with left ventricular hypertrophy are prone to subendocardial ischemia, even in the absence of ischemic heart disease. Ischemia increases myocardial diastolic stiffness and exacerbates diastolic dysfunction. Because most coronary flow occurs in diastole, tachycardia with reduced diastolic filling time compromises subendocardial perfusion. Heart rate control is therefore central to preventing or treating ischemia associated with heart failure and preserved systolic function. β-Blockers and some calcium channel blockers (e.g., verapamil) are useful negative chronotropic agents. For patients with ischemic heart disease, percutaneous or surgical revascularization may be indicated to treat ischemia.

Pulmonary venous congestion associated with diastolic dysfunction usually responds rapidly to preload reduction with diuretics and/or nitrates. Because of increased myocardial stiffness, however, a small decreases in left ventricular volume can cause marked decreases in left atrial filling pressure, stroke volume, and cardiac output. It is, therefore, important to avoid excessive preload reduction, which can cause symptomatic hypotension, especially in the elderly. Diuretic therapy should be initiated with a small dose of a loop diuretic (e.g., furosemide 20 mg, bumetanide 0.5 mg). If effective diuresis is not achieved, the dose should be increased or a second diuretic agent (e.g., metolazone 2.5 to 5 mg) may be added.

Table 14–12 Morbidity and Mortality Trials in Heart Failure with Preserved Systolic Function

Study	N	Agent	Entry Criteria	Primary Endpoint	Expected Completion
I-PRESERVE[231]	4128	Irbesartan vs. placebo	Age ≥ 60 LVEF ≥ 45%	All-cause death or CV hospitalization	2007
PEP-CHF[232]	1000	Perindopril vs. placebo	Age ≥ 70 LVEF ≥ 40%	All-cause death or HF hospitalization	NA
TOPCAT[233]	4500	Spironolactone vs. placebo	Age ≥ 50 LVEF ≥ 45%	CV death or HF hospitalization	2011

CV, cardiovascular; HF, heart failure; I-PRESERVE, Irbesartan in Heart Failure with Preserved Systolic Function; LVEF, left ventricular ejection fraction; NA, not available; PEP-CHF, Perindopril for Elderly Patients with Chronic Heart Failure; TOPCAT, Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure.

Because of increased left ventricular diastolic stiffness, some patients with heart failure and normal ejection fraction have reduced passive ventricular filling in early and mid-diastole and depend on an active atrial contribution to late ventricular filling. Thus, there has been a strong rationale for maintaining sinus rhythm to achieve adequate stroke volume and cardiac output. Trials that have tested rate versus rhythm control strategies in atrial fibrillation have failed to demonstrate benefits of rhythm control and show higher rates of hospitalization and adverse drug effects.[176] Unfortunately, these trials have included few patients with heart failure. Until data from ongoing clinical trials are available, β-blockers, calcium channel blockers, or digoxin may be used alone or in combination to control the ventricular response. If rate control is ineffective, treatment options are chemical or electrical cardioversion, catheter ablation of atrial fibrillation (i.e., pulmonary vein isolation), or ablation of the atrioventicular junction with pacemaker implantation.[177] All patients with persistent or paroxysmal atrial fibrillation should receive anticoagulation therapy unless there is a contraindication to warfarin.

In general, positive inotropic agents should not be used in patients with heart failure and preserved systolic function because these agents may adversely affect myocardial energetics, induce ischemia, and promote tachyarrhythmias. In the DIG ancillary study, the addition of digoxin to patients with heart failure and an ejection fraction greater than 45% tended to reduce the combined endpoint of death or hospitalization due to worsening heart failure (risk ratio, 0.82; 95% CI, 0.63 to 1.07) but had no effect on all-cause mortality.[108]

Patients with Ischemic Heart Disease

There are several ways in which ischemic heart disease can complicate the management of heart failure. Symptoms of angina pectoris and myocardial ischemia are often difficult to distinguish from the exertional dyspnea and fatigue associated with heart failure. However, patients who have myocardial ischemia frequently require additional anti-ischemic therapy to maximize clinical status. Therefore, in addition to standard treatment with renin-angiotensin system inhibitors, β-blockers, and diuretics, these patients may improve further with the addition of nitrates. Ranolazine, an inhibitor of the slow inactivating sodium current (I_{Na}), has also been approved for the treatment of chronic angina (see Appendix 1).[178] The safety and efficacy of ranolazine have not been tested in heart failure, but there is theoretical reason to believe that late I_{Na} inhibition could improve myocardial efficiency and lead to functional benefits,[179] although this remains unproven.

Other patients with ischemic heart disease may have periodic decompensations that are triggered by episodes of myocardial ischemia. In addition to anti-ischemic pharmacotherapy, these patients may benefit from coronary revascularization, with either coronary artery bypass graft surgery or percutaneous coronary intervention. An important therapeutic consideration in these patients is the presence of hibernating myocardium.[180] Many patients will experience marked improvement in left ventricular function following bypass surgery, and assessment of myocardial viability appears to be an important tool in predicting which patients will have a favorable response.[181] The role of surgical revascularization with or without ventricular reconstruction in patients with ischemic cardiomyopathy is discussed in Chapter 16. For patients with ischemia not amenable to direct revascularization, enhanced external counterpulsation (EECP) may reduce angina and improve exercise tolerance and quality of life; however, the mechanisms responsible for the therapeutic response and the impact on long-term morbidity and mortality rates remain unknown.[182] For selected patients with end-stage ischemic cardiomyopathy, heart transplantation may be the preferred option (see Chapter 18).

Patients with Valvular Heart Disease

Patients with significant regurgitant valvular heart disease represent another difficult patient subgroup. Many patients with significant left ventricular dilatation will have functional mitral regurgitation due to annular dilatation. Other patients will have concomitant pathology of the mitral apparatus due to a history of rheumatic heart disease, myxomatous degeneration, or ischemic heart disease and papillary muscle dysfunction. Frequently, the use of vasodilator and diuretic therapy will adequately reduce the regurgitant volume resulting in hemodynamic and symptomatic improvement, which may be long lasting.[183] In other cases, in which abnormalities of the mitral valve or subvalvular apparatus make a primary contribution to symptoms and left ventricular dysfunction, valve repair or replacement may have important therapeutic benefit. However, there is no reliable method to distinguish consistently those patients who will benefit from mitral valve surgery from those who experience a progressive decline in ventricular function after mitral surgery. Mitral valvuloplasty

has also been performed safely in patients with dilated cardiomyopathy and severe mitral regurgitation due to annular dilatation with encouraging results in uncontrolled studies.[184] However, the long-term benefits of mitral valve repair compared with medical therapy in this subset of patients remain unproved.[101] Novel devices for percutaneous mitral valve repair are under development.[185]

Patients with Diabetes

Overall, diabetes is present in 20% to 30% of patients with heart failure, and there are several concerns about pharmacologic treatment of diabetes in heart failure patients. The thiazolidinedione (TZD) class of oral hypoglycemic agents has gained widespread popularity for the treatment of insulin resistance owing to several advantageous ancillary effects on lipid metabolism, vascular endothelial function, and inflammatory cytokines.[186] However, these agents may increase fluid retention and exacerbate heart failure symptoms. In general, TZDs produce a 6% to 7% increase in circulating intravascular volume and a 2- to 4-kg weight gain. In a study of diabetic patients with heart failure, initiation of TZDs was associated with a 17% increase in fluid retention as defined by a 10-pound involuntary weight gain.[187] Risk factors include older age, hypertension, and ischemic heart disease. TZD-induced fluid retention is dose-related and exacerbated by concomitant insulin use. Peripheral rather than central edema predominates and usually resolves on drug withdrawal. These agents are contraindicated in patients with NYHA functional class III-IV heart failure and should be used with caution in mild heart failure.

Metformin is another popular oral insulin sensitizer. According to the package insert, metformin is contraindicated in patients with “heart failure requiring pharmacological therapy” because of the risk of lactic acidosis.[188] Although the overall incidence of life-threatening lactic acidosis is low, the U.S. Food and Drug Administration assigned a black box warning in response to post-marketing reports of increased risk among patients with chronic hypoperfusion and hypoxia. Despite cautionary alerts, a review of prescribing patterns among Medicare beneficiaries hospitalized with heart failure reported that nearly one fourth of patients were discharged on either a TZD or metformin.[188] Given the increased awareness of the beneficial cardiovascular effects of these agents when used in the general population, further data are needed to examine their risk-benefit ratio in patients with heart failure.

Gender, Race, and Ethnic Considerations

With few exceptions, blacks and some other racial minorities and women have been underrepresented in randomized controlled trials of new treatments for heart failure. However, most subgroup and meta-analyses have shown consistent benefits of standard therapy across a broad range of patient populations.[66] ACE inhibitors, angiotensin receptor blockers, β-blockers, and spironolactone are equally effective in men and women with symptomatic left ventricular dysfunction, whereas data on digoxin have been conflicting. In a post-hoc subgroup analysis of the DIG trial, Rathore and associates[189] found that women who were randomized to digoxin had a higher mortality rate compared with women who received placebo (33.1% versus 28.9%), an effect that was not seen in men. Additional analyses, however, suggested that this gender-treatment interaction may have been attributed to higher serum digoxin concentrations in women.[113] Other treatment recommendations specific to women with heart failure include avoiding ACE inhibitors, angiotensin receptor blockers and Coumadin (warfarin) during pregnancy, and exercising caution in the use of cardiotoxic chemotherapy (e.g., trastuzumab) in the treatment of breast cancer. For men with heart failure and erectile dysfunction, intermittent use of PDE type 5 inhibitors (e.g., sildenafil, vardenafil) appears safe and effective.[190]

Compared with whites, blacks appear to develop heart failure at an earlier age and to have more rapid progression of symptoms.[191] The increased awareness of these differences in heart failure epidemiology has led to a greater emphasis by heart failure specialists in defining the most effective therapy in blacks. Although retrospective analyses suggest that blacks with hypertension or heart failure experience less efficacy with ACE inhibitors, a current meta-analysis demonstrated similar mortality reduction in blacks and nonblacks with heart failure.[66] The data from randomized controlled trials of β-blockers are less clear with carvedilol showing equal efficacy in black and nonblack patients,[80] whereas bucindolol tended to increase morbidity and mortality rates in blacks.[91] Excluding results from the BEST trial, Shekelle and colleagues[66] analyzed race-stratified data on β-blockers from the COPERNICUS, MERIT-HF, and U.S. Carvedilol studies and found that the relative risk on the effect of mortality for black patients was 0.67 (95% CI, 0.38 to 1.16). As discussed earlier, the combination of hydralazine and isosorbide dinitrate reduces morbidity and mortality rates in self-identified blacks with symptomatic left ventricular systolic dysfunction, and is now recommended as part of standard therapy in addition to ACE inhibitors and β-blockers.[192]

Like Blacks, Hispanics and other ethnic minorities have received little attention in heart failure trials. In the absence of data showing lack of efficacy or excess toxicity, renin-angiotensin-aldosterone system inhibitors, β-blockers, and other pharmacologic agents used to treat heart failure should be prescribed according to indications outlined in this chapter and national guidelines.[4,192]

Patients with Myocarditis

The underlying causes, pathophysiology, clinical manifestations, and diagnostic evaluation of myocarditis are discussed in detail in Chapter 60 in HD7e and other reviews.[193] In brief, myocarditis is a rare disease for which pathophysiologic mechanisms are not well understood, and for which there is no diagnostic “standard” or proven therapy. Primary myocarditis is believed to be the result of viral and post-viral immunologic effects on the heart,[193] and most therapies have been aimed at modulating the immune response. For patients with secondary myocarditis, inflammation of the myocardium due to a known agent (e.g., *Aspergillus*, mycobacterium tuberculosis) frequently resolves with treatment of the causative agent.

Most patients with myocarditis have a history of an acute viral illness, although there is usually a delay between the initial viral symptoms and the onset of symptoms of heart muscle disease. This delay is probably dependent on the viral etiology and host response. Adults with fulminant myocarditis display the least delay and present with severe heart failure.[194] Rarely, patients may present with embolic phenomena, such

as myocardial infarction or sudden death. Although acute and convalescent viral titers may be of some value in determining the most likely cause of myocarditis, these tests suggest only an association and do not establish the diagnosis. Furthermore, noninvasive nuclear imaging studies with gallium or antimyosin antibody have relatively high false-negative rates and are too nonspecific to be of diagnostic use.[195] The diagnosis of myocarditis can be established by endomyocardial biopsy and requires evidence of myocyte damage associated with an inflammatory cell infiltrate not typical of damage caused by ischemic heart disease. Because of sampling error, the false-negative rate of endomyocardial biopsy to diagnose myocarditis may be as high as 30% when up to five specimens are obtained.[196]

Currently, there are no clinically available antiviral agents for treating the enteroviruses (coxsackieviruses B and A, echovirus, and adenovirus) that cause most cases of primary myocarditis. In addition, immunization to prevent myocarditis is impossible because of the large number of potential causative agents. Because most cases of myocarditis are believed to be immune-mediated, immunosuppressive agents have received the most attention in the search for effective therapy. However, the results of controlled trials have been disappointing.[197-199]

The rate and degree of improvement in ventricular performance that have been observed in uncontrolled trials of immunosuppressive therapy have raised the possibility that many patients with myocarditis recover spontaneously. The Myocarditis Treatment Trial was a prospective, randomized National Institutes of Health-supported study that sought to determine the effect of immunosuppressive therapy on left ventricular function in patients with myocarditis.[198] More than 2200 patients who presented with heart failure of less than 2 years' duration and an ejection fraction of less than 45% underwent endomyocardial biopsy. Two hundred patients (≈10%) had biopsy-proven myocarditis, and of these, only 111 were randomized to receive conventional therapy alone or combined with prednisone and either cyclosporine or azathioprine. After 28 weeks of therapy, the mean left ventricular ejection fraction increased from 25% to 34% in the group as a whole but did not differ significantly between the groups. In addition, there was no difference in survival with overall 1- and 4-year mortality rates of 20% and 56%, respectively. Another immunomodulatory therapy that has been proposed for the treatment of myocarditis based on preclinical and uncontrolled clinical studies is intravenous immune globulin (IVIG).[200] However, a randomized controlled trial of IVIG (2 gm/kg) in 62 patients with new onset heart failure and an ejection fraction of 40% or less failed to show a benefit over placebo.[199] The mean ejection fraction increased dramatically in the group as a whole (from 25% to 42%), and prognosis was excellent with a 2-year event-free survival of 88%.

Based on these results, many referral centers have become less aggressive in performing endomyocardial biopsy to diagnose myocarditis given the lack of proven therapy.[201] In addition, there are data showing no difference in survival between patients with myocarditis and those with idiopathic dilated cardiomyopathy.[202] However, in the subgroup of patients who present with hemodynamic compromise, endomyocardial biopsy to confirm a diagnosis of fulminant myocarditis versus giant cell or hypersensitivity myocarditis can have important prognostic and therapeutic implications. Adults with fulminant lymphocytic myocarditis respond poorly to immunosuppressive therapy but may benefit from aggressive hemodynamic support, including mechanical cardiac assist, as a "bridge" to recovery.[194] By contrast, patients with giant cell myocarditis have a poor prognosis and should be urgently evaluated for mechanical assist and transplant.[203] New understanding of disease mechanisms will hopefully lead to improved diagnostic and therapeutic strategies for myocarditis.[204]

FUTURE DIRECTIONS IN PHARMACOLOGIC THERAPY

Future directions for heart failure therapy include novel neurohormonal antagonists, modulation of myocardial energetics, and treatment of comorbidities such as anemia and pulmonary hypertension (see Table 14–9). Plasma levels of arginine vasopressin are elevated in patients with heart failure and may contribute to disease progression through stimulation of V_{1a} and V_2 receptors, causing vasoconstriction and free-water retention, respectively.[205] Short-term administration of vasopressin receptor antagonists in patients with decompensated heart failure improves hemodynamics and increases urine output without adversely effecting electrolytes or renal function.[206,207] The effect of chronic vasopressin receptor blockade on clinical outcomes is currently being tested in controlled clinical trials.[208] Like vasopressin, adenosine may contribute to maladaptive volume regulation in patients with coexistent cardiac and renal failure. Adenosine mediates intrarenal vasoconstriction and inhibition of tubuloglomerular feedback via stimulation of A_1 receptors.[209] In pilot studies, selective A_1 receptor antagonists show modest diuretic effects but offer the potential to attenuate diuretic-induced worsening of renal function.[210] Controlled trials are currently underway to determine the safety and efficacy of these agents in patients with advanced heart failure.

Another novel neurohormonal approach to managing patients with chronic decompensated heart failure is intermittent outpatient infusions of natriuretic peptides.[211] Although these compounds cause modest diuresis and natriuresis, improve hemodynamics, and inhibit neurohormonal activation acutely, their long-term effects on ventricular remodeling and disease progression remain unproven. Finally, modulation of myocardial energetics is also emerging as a novel therapeutic target in cardiovascular disease.[179] Anti-anginal agents such as trimetazidine and ranolazine may increase cardiac performance in heart failure without dependence on changes in oxygen consumption or improvement in hemodynamics.

Recognition and treatment of comorbidities are also a major focus of ongoing investigation in heart failure. Anemia is common in heart failure and may be caused by increased plasma volume or decreased red cell mass.[212] Contributing factors include malnutrition with iron deficiency, bone marrow suppression from activation of pro-inflammatory cytokines, and chronic kidney disease. Anemia may contribute to ventricular remodeling and disease progression by stimulating neurohormonal and cytokine activation, promoting left ventricular hypertrophy, and exacerbating ischemia. Short-term studies of erythropoietin have shown that correction of anemia improves exercise tolerance and quality of life.[213] The effects of erythropoietic agents on morbidity and mortality rates in heart failure are currently being tested in a large, controlled trial.

Like anemia, secondary pulmonary hypertension is common in patients with advanced heart failure and is associated with exercise intolerance and adverse outcomes.[214] Dysregulation of pulmonary vascular tone and structural remodeling are caused, in part, by pulmonary vascular endothelial dysfunction that results in impaired nitric oxide availability and decreased levels of cyclic guanosine-monophosphate (cGMP).[215] PDE-5 inhibitors such as sildenafil cause pulmonary vasodilation by promoting an enhanced and sustained level of cGMP. In patients with pulmonary arterial hypertension, acute administration of sildenafil decreases pulmonary vascular resistance and increases cardiac index.[216] The long-term effects of sildenafil in patients with heart failure and secondary pulmonary hypertension remain to be tested, although intermittent use of PDE-5 inhibitors appears to be safe in heart failure patients with erectile dysfunction.[190] Use of PDE-5 inhibitors is contraindicated in patients receiving organic nitrates for treatment of ischemic heart disease or heart failure.

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Chapter 15

Implantable Devices for the Management of Heart Failure

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CHAPTER CONTENTS

Following decades focused on pharmacologic management, the year 2001 ushered in a new era of implantable device therapies for the management of heart failure with the U.S. Food and Drug Administration (FDA) approval of the first cardiac resynchronization therapy (CRT) device. Soon thereafter, randomized controlled trials were published that supported the routine use of implantable cardioverter-defibrillators (ICDs) and of combined CRT-ICD devices in the management of heart failure (HF). Although ICDs had already been indicated for the management of resuscitated cardiac arrest, ventricular fibrillation, and hemodynamically destabilizing ventricular tachycardia in HF patients, these newer studies demonstrated mortality reduction with the prophylactic use of an ICD, substantially enlarging the population of patients eligible for an ICD. By 2005, the strength of evidence supporting the use of an ICD or CRT with or without a defibrillator in the management of HF was sufficiently strong to recommend use of these therapies in all eligible patients.[1]

In addition to the therapeutic benefits of CRT and ICDs, implantable devices that monitor HF clinical status and/or hemodynamics have been developed and are now under investigation. One such device has recently been approved by the FDA. Using measurement of intrathoracic impedance, an available CRT-ICD device can track intrathoracic fluid volume changes. Although the usefulness of this measurement is incompletely understood, preliminary findings suggest that intrathoracic impedance changes can predict episodes of worsening HF and provide an opportunity to prevent them. This strategy is now under investigation in large randomized controlled trials. Another investigational approach to managing HF is through the use of implantable hemodynamic monitoring systems. These systems enable the day-to-day management of ventricular filling pressures and other physiologic parameters, not otherwise available to the clinician. Early reports suggest a substantial opportunity to reduce HF morbidity rates (e.g., episodes of worsening HF requiring hospitalization), with the use of these devices.

This chapter reviews the use of ICDs and CRT for the management of HF, previews the promise of implantable HF monitoring devices, and mentions other investigational device therapies for HF.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS IN THE MANAGEMENT OF HEART FAILURE

Implantable cardioverter-defibrillators were initially applied to survivors of sudden cardiac death (SCD) to treat second episodes of ventricular tachycardia or ventricular fibrillation (see Chapter 21 for complete discussion of ICD use in secondary prevention of SCD). Patients with left ventricular dysfunction, either from ischemic or nonischemic etiologies, are at increased risk for SCD.[2,3] SCD is the leading cause of mortality in patients with HF and occurs at a rate six-to-nine times that seen in the general population. The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) showed that patients with New York Heart Association (NYHA) functional class II or III symptoms die most frequently as a result of SCD.[4] This study estimated the proportion of total mortality attributable to SCD at 64% and 59% for NYHA classes II and III patients, respectively. In contrast, the major cause of death in class IV patients in MERIT-HF was progressive or endstage HF. Thus, all but the sickest HF patients are more likely to die suddenly rather than from worsening HF.

On this background, a series of studies has expanded the use of ICDs as prophylactic therapy in at-risk subjects (see Tables 21–3 and 21–5).[5-10] These studies have focused mainly on patients with coronary artery disease (usually after myocardial infarction [MI]) and/or more recently on those with left ventricular systolic dysfunction of any cause. In the HF/left ventricular dysfunction population, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) was the

first primary prevention study to show the benefit of prophylactic ICD implantation.[5] High-risk patients (N = 196) with prior MI, left ventricular ejection fraction of 35% or less, nonsustained ventricular tachycardia of 3 to 30 beats at a rate >120/minute underwent electrophysiologic testing and were randomized to an ICD versus conventional antiarrhythmic therapy (primarily amiodarone). Compared with conventional therapy, the ICD arm demonstrated an impressive reduction in all-cause mortality at 2 years (15.8% versus 38.6%, P = 0.009). However, significantly more patients in the ICD group were receiving treatment with a β-blocker, confounding the results of the trial.

MADIT was followed by a number of other encouraging studies of left ventricular systolic dysfunction patients, such as the CABG-Patch trial and the Multicenter Unsustained Tachycardia Trial (MUSTT).[6,7] However, the landmark trials establishing a role for ICDs as primary prevention of mortality in HF patients are MADIT II and the National Institutes of Health-sponsored Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT).[8,10] Although underpowered to demonstrate a significant difference for its primary endpoint, the Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy (DEFINITE) trial also contributed substantially to the burden of proof supporting prophylactic intervention with an ICD in the management of HF.[9]

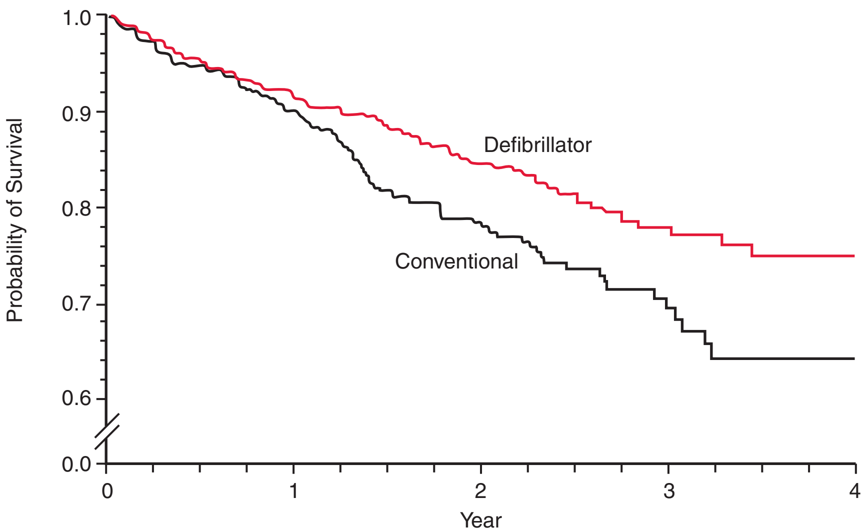
MADIT II

MADIT II, a randomized controlled trial, was prospectively designed and powered to assess the survival benefit of ICDs in a population of post-MI patients with reduced ejection fraction (<30%). Importantly, this trial included no arrhythmic markers such as nonsustained or inducible ventricular tachycardia for inclusion. A total of 1232 patients were randomly assigned in a 3:2 ratio to receive an ICD (742 patients) or conventional medical therapy (490 patients). During an average follow-up of 20 months, the all-cause mortality rates were 19.8% in the conventional therapy arm and 14.2% in the ICD group (31% relative risk reduction, P = 0.016) (Fig. 15–1). The effect of ICD therapy on survival was similar in subgroup analyses stratified according to age, gender, ejection fraction, NYHA class, and the QRS interval. Moreover, β-blocker use was 72% in these patients and was well balanced between the ICD and conventional therapy groups.

Of note, the majority of patients enrolled into MADIT II were classified in NYHA class II or III. NYHA class IV patients were excluded and the NYHA class I cohort was relatively small. The average left ventricular ejection fraction was 23%. These findings suggest that HF patients with mild-to-moderate symptoms and moderate-to-severe reduction in left ventricular ejection fraction may benefit the most from a prophylactic ICD. Moreover, in contrast to MADIT I where the survival benefit of ICD therapy was seen early post-randomization, the survival benefit observed in MADIT II began approximately 9 months after the device was implanted. The authors suggested that this difference may be due to a lower risk population being enrolled in MADIT II, the absence of arrhythmia as risk stratification for entry, and/or the use of more aggressive medical treatment. Regardless of the explanation, this observation may be important when considering the timing of device placement in eligible patients.

DEFINITE

Whereas MADIT II enrolled exclusively post-MI patients with an ischemic cause of left ventricular systolic dysfunction and HF, the DEFINITE trial was the first randomized trial of primary prevention therapy with an ICD in nonischemic cardiomyopathy patients.[9] Such patients also exhibit high rates of SCD; however, there has been little consensus regarding the management of SCD risk in such patients. This may be due, in part, to limitations in objective risk assessment, in that no invasive or noninvasive testing procedure has been shown to accurately determine which nonischemic HF patient is likely to die suddenly. Also clouding the picture were older observa-



No. at Risk

Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Figure 15–1 Kaplan-Meier estimates of survival in patients randomized to an ICD compared with conventional medical therapy in the MADIT II trial. P = 0.007 by log-rank test.

tions suggesting that the prophylactic administration of an antiarrhythmic agent, amiodarone, might prolong survival in nonischemic cardiomyopathy patients.[11]

The DEFINITE trial was a prospective evaluation of 458 patients with nonischemic dilated cardiomyopathy. Entry criteria included an ejection fraction of ≤35%, a history of symptomatic HF, and the presence of ambient arrhythmias defined as an episode of nonsustained ventricular tachycardia or at least ten premature ventricular contractions per 24-hour period on continuous ambulatory electrocardiographic monitoring. Patients (N = 229) were equally randomized to each arm of the study to receive either an ICD and standard medical therapy or standard medical therapy alone. Compliance with medical therapy was excellent and included an angiotensin-converting enzyme inhibitor (ACE-I) in 86% of the cohort and a β-blocker in 85%. The patients were followed for a mean of 29.0 ± 14.4 months with a primary endpoint of all-cause mortality.

There were 68 deaths reported in the DEFINITE trial, 28 in the ICD group, and 40 in the standard therapy group. The implantation of an ICD yielded a nonsignificant 35% reduction in death from any cause (hazard ratio, 0.65; 95% CI, 0.40 to 1.06; P = 0.08) and significantly reduced the risk of sudden death by a remarkable 80% (hazard ratio, 0.20; 95% CI, 0.06 to 0.71; P = 0.006). In the subgroup of NYHA class III patients, all-cause mortality was significantly decreased in the ICD arm (hazard ratio, 0.37, 95% CI 0.15 to 0.90; P = 0.02).

Although this study was underpowered and did not reach statistical significance with respect to the primary endpoint of all-cause mortality for the entire randomized cohort, the results demonstrated a strong trend toward a survival advantage for patients receiving an ICD. It is worth mentioning that the all-cause mortality reduction seen in DEFINITE was 35%, a value that is strikingly similar to the 31% relative risk reduction observed in the ischemic population studied in MADIT II. The statistical power of DEFINITE was affected by a low rate of SCD in both groups, which may be related to aggressive use of ACE-I and β-blockade in this trial.

SCD-HeFT

The results of the SCD-HeFT trial were published in 2005 and have had a substantial impact on current practice and reimbursement guidelines for ICDs.[10] This landmark randomized controlled trial enrolled 2521 patients from 148 mostly U.S. centers between 1997 and 2001. Patients with NYHA class II (70%) or III (30%) HF and reduced left ventricular ejection fraction (35% or less, mean about 25%) of either ischemic or nonischemic etiology were eligible for the study. SCD-HeFT was a three-arm trial, comparing treatment with an ICD with amiodarone and placebo. Thus, SCD-HeFT addressed at least two important issues in HF management: (1) whether or not empirical amiodarone therapy saved lives in well-treated NYHA classes II and III HF patients with no arrhythmic indication for the drug and (2) whether or not a prophylactic ICD saved lives in such patients with HF from either an ischemic or nonischemic cause.

In SCD-HeFT, patients received standard HF therapy, if tolerated, which included an ACE-I or angiotensin receptor blocker in 85%, β-blocker in 69%, and aldosterone antagonists in 19%, compatible with guidelines recommendations at the time the study was conducted. The median follow-up was 45.5 months. Importantly, the cohort was equally divided between ischemic and nonischemic causes of HF, allowing an important subgroup analysis of these cohorts to be done.

Mortality rates in the ICD, amiodarone, and placebo groups were 17.1%, 24%, and 22.3%, respectively, at 3 years and 28.9%, 34.1%, and 35.9%, respectively, at 5 years. The ICD was associated with a statistically significant 23% reduction in all-cause mortality compared with placebo (hazard ratio 0.77; 97.5% CI, 0.62 to 0.96, P = 0.007). Outcomes on amiodarone were not significantly different from placebo across all subgroups (hazard ratio 1.06; 97.5% CI, 0.86 to 1.30). Similar degrees of benefit were noted in patients with ischemic (21% mortality reduction) and nonischemic (27% mortality reduction) HF, thus confirming the findings of MADIT II and DEFINITE, respectively. The SCD-HeFT trial provides the most robust evidence to date supporting the prophylactic use of ICDs in patients with NYHA classes II and III systolic HF of virtually any cause.

INDICATIONS FOR PROPHYLACTIC CARDIOVERTER-DEFIBRILLATOR IMPLANTATION IN HEART FAILURE PATIENTS

Based on these trials, the indication for an ICD has been extended to NYHA classes II and III HF patients with a reduced ejection fraction (see Chapter 21). The 2005 ACC/AHA HF guidelines promote class I indications for the use of an ICD as primary prevention of all-cause mortality in well-treated NYHA classes II and III patients with a left ventricular ejection fraction of 30% or less and either ischemic or nonischemic cardiomyopathy.[1] There is a class IIa indication for such patients with ejection fractions of 31% to 35%. The reasoning behind these separate indications stems from the fact that MADIT II and SCD-HeFT used different ejection fraction criteria for enrollment. In any event, patients with moderate-to-severe left ventricular systolic dysfunction and NYHA class II or III HF should receive an ICD, unless there are mitigating circumstances or a contraindication to the implantation or use of this device. In this regard, the ACC/AHA guidelines qualify that ICD candidates should have a reasonable expectation of survival with a good functional status for more than 1 year, and the Centers for Medicare and Medicaid Services require waiting 3 months after surgical or percutaneous revascularization.

Practical Considerations in ICD Therapy

Before ICD implantation, patients should have a thorough understanding of the risks and benefits of device therapy, including the need for routine follow-up and defibrillation threshold testing and the morbidity associated with appropriate and inappropriate ICD shocks. Patients should understand that an ICD has been shown to prolong survival, but will not improve HF symptoms or slow disease progression. It should also be explained to the patient and family that the defibrillator function of an implantable device can be turned off as part of end-of-life care. Questions regarding exercise, driving, cellular telephones, and airport security, among others, should be anticipated and addressed in advance.

The management of complications after ICD implantation is discussed in Chapter 21. Monitoring for bleeding or infection is paramount during the early post-implant period, although seeding of the device from a distant infectious source may occur at anytime. For patients who develop new or recurrent ventricular arrhythmias that cause frequent ICD shocks, therapeutic options include antiarrhythmic drugs such as amiodarone or mexiletine, catheter ablation of ventricular tachycardia, or, in selected cases, consideration of mechanical cardiac assist or transplant. In patients with ischemic heart disease, the occurrence of polymorphic ventricular tachycardia that leads to ICD shocks should warrant reassessment for ischemia. Patients who develop significant anxiety related to ICD shocks may benefit from anxiolytic therapy and/or referral to a therapist or support group. Finally, it is important to remember that ICDs may aggravate HF as a result of mechanical dyssynchrony induced by right ventricular pacing.[12]

CONDUCTION ABNORMALITIES IN HEART FAILURE

A number of conduction abnormalities are seen in the setting of chronic HF. Approximately one third of patients with systolic HF have a QRS duration >120 msec, which is most commonly seen as a left bundle branch block (LBBB).[13,14] Such conduction delays produce suboptimal ventricular filling, a reduction in left ventricular contractility, prolonged duration of mitral regurgitation, and paradoxical septal wall motion.[15-18] These mechanical manifestations of ventricular conduction abnormalities have been referred to as ventricular dyssynchrony, especially because the septum and left ventricular free wall no longer contract in a normal near-simultaneous fashion. This situation reduces the ability of the failing heart to eject blood and has been associated with increased mortality in HF patients.[19-22]

In the mid-1990s, the application of pacing therapies to overcome ventricular dyssynchrony began to be explored. In particular, atrial-synchronized biventricular pacing—now known as cardiac resynchronization therapy or CRT—emerged as the most promising approach for the treatment of ventricular dyssynchrony. A series of studies confirmed the benefits of CRT in NYHA functional classes III and IV HF patients with ventricular dyssynchrony and led to a strong contemporary recommendation for the use of this therapy.[1]

The first application of atrial-synchronized biventricular pacing was performed by Cazeau and colleagues[23] who used four-chamber pacing in a 54-year-old man with NYHA class IV HF and significant atrial-ventricular and ventricular conduction disturbances. Standard transvenous pacing leads were placed in the right atrium and right ventricle. The left atrium was paced by a lead placed in the coronary sinus, whereas the left ventricle was paced by an epicardial lead located on the left ventricular free wall. After 6 weeks of pacing, the patient's clinical status improved markedly, with a weight loss of 17 kg and a disappearance of peripheral edema. His functional class improved remarkably to NYHA class II. Such favorable anecdotal experiences led to the inception of small studies to evaluate the acute effects of biventricular pacing on systemic hemodynamics. These studies provided additional proof of concept that CRT might reverse the deleterious consequences of ventricular dyssynchrony.[17,24] Several studies soon followed to further evaluate the acute and longer-term effects of biventricular pacing in HF.[25-33] The results were equally encouraging, with patients showing consistent, sustained improvement in exercise tolerance, quality of life, NYHA functional class, and cardiac output. With the advent of a transvenous rather than an epicardial approach for biventricular pacing, larger-scale observational and randomized controlled trials of CRT were made possible.

LANDMARK CARDIAC RESYNCHRONIZATION THERAPY CLINICAL TRIALS

Substantial evidence supports the beneficial effects of CRT for the treatment of HF. Approximately 4000 patients have been evaluated in randomized single- or double-blind controlled trials, including large-scale morbidity and mortality studies. The most important of these trials are the Multisite Stimulation in Cardiomyopathy (MUSTIC) studies,[34,35] the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial,[36,37] MIRACLE ICD,[38] the CONTAK CD trial,[39] the Cardiac Resynchronization in Heart Failure (CARE HF) trial,[40,41] and the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.[42,43]

MUSTIC

The MUSTIC trials were designed to evaluate the safety and efficacy of cardiac resynchronization in patients with advanced HF, ventricular dyssynchrony, and either normal sinus rhythm[34] or atrial fibrillation.[35] They represent the first randomized single-blind trials of CRT for HF. The first study involved 58 randomized patients with NYHA class III HF, normal sinus rhythm, and a QRS duration of at least 150 msec. All patients were implanted with a CRT device, and after a run-in period, patients were randomized in a single-blind fashion to either active pacing or to no pacing. After 12 weeks, patients were crossed over and remained in the alternate study assignment for 12 weeks. After completing this second 12-week period, the device was programmed to the patient's preferred mode of therapy. The second MUSTIC study involved fewer patients (only 37 completers) with atrial fibrillation and a slow ventricular rate (either spontaneously or from radiofrequency ablation). A VVIR biventricular pacemaker and leads for each ventricle were implanted, and the same randomization procedure just described was applied; however, biventricular VVIR pacing versus single-site right ventricular VVIR pacing (rather than no pacing) was compared in this group of patients with atrial fibrillation.

The primary endpoints for MUSTIC were exercise tolerance assessed by measurement of peak $\dot{V}O_2$ or the 6-minute hall walk test and quality of life determined using the Minnesota Living with Heart Failure questionnaire. Secondary endpoints included rehospitalizations and/or drug therapy modifications for worsening HF. Results from the normal sinus rhythm arm of MUSTIC provided strong evidence of benefit. The mean distance walked in 6 minutes was 23% greater with CRT than during the inactive pacing phase ($P < 0.001$). Significant improvement was also seen in quality of life and NYHA functional class ranking. There were fewer

hospitalizations during active resynchronization therapy. The atrial fibrillation cohort evaluated in MUSTIC demonstrated similar improvements, although the magnitude of benefit was slightly less.

MIRACLE

MIRACLE was the first prospective, randomized, double-blind, parallel-controlled clinical trial designed to evaluate the merits of CRT and to further elucidate potential mechanisms of action of CRT.[36,37] Primary endpoints were NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire), and 6-minute hall walk distance. Secondary endpoints included assessments of a composite clinical response, cardiopulmonary exercise performance, neurohormone and cytokine levels, QRS duration, cardiac structure and function (as determined by echocardiography), and a variety of measures of worsening HF and combined morbidity and mortality.

The MIRACLE trial was conducted between 1998 and 2000. Patients (N = 453) with moderate-to-severe symptoms of HF associated with a left ventricular ejection fraction ≤35% and a QRS duration of at least 130 msec were randomized (double-blind) to cardiac resynchronization (n =228) or to a control group (n = 225) for 6 months, while conventional therapy for HF was maintained.[37] Compared with the control group, patients randomized to CRT demonstrated a significant improvement in quality-of-life score (–18.0 versus –9.0 points, P = 0.001), 6-minute walk distance (+39 versus +10 meters, P = 0.005), NYHA functional class ranking (–1.0 versus 0.0 class, P < 0.001), treadmill exercise time (+81 versus +19 sec, P = 0.001), peak $\dot{V}O_2$ (+1.1 versus 0.1 mL/kg/min, P < 0.01), and left ventricular ejection fraction (+4.6% versus –0.2%, P < 0.001) (Fig. 15–2). Patients randomized to CRT demonstrated a highly significant improvement in a composite clinical HF response endpoint compared with control subjects, suggesting an overall improvement in HF clinical status. In addition, when compared with the control group, fewer patients in the CRT group required hospitalization (8% versus 15%) or intravenous medications (7% and 15%) for the treatment of worsening HF (both P < 0.05). In the resynchronization group, the 50% reduction in hospitalization was accompanied by a significant reduction in length of stay, resulting in a 77% decrease in total days hospitalized over 6 months compared with the control group. The major limitation of the therapy was caused by unsuccessful implantation of the device in 8% of patients. The results of this trial led to the FDA approval of the InSync system in August 2001, the first approved CRT system in the U.S., allowing the introduction of CRT into clinical practice.

The MIRACLE trial also provided persuasive evidence supporting the occurrence of reverse left ventricular remodeling with chronic CRT. In the MIRACLE Trial, serial Doppler echocardiograms were obtained at baseline, 3, and 6 months in a subset of 323 patients.[44] Cardiac resynchronization therapy for 6 months was associated with reduced end-diastolic and end-systolic volumes (both P < 0.001), reduced left ventricular mass (P < 0.01), increased ejection fraction (P < 0.001), reduced mitral regurgitant blood flow (P < 0.001), and improved myocardial performance index (P < 0.001) as compared with controls. These effects are similar to those seen with β-blockade in HF but were seen in MIRACLE in patients already receiving β-blocker therapy.

MIRACLE ICD

The MIRACLE ICD study was designed to be almost identical to the MIRACLE trial. MIRACLE ICD was a prospective, multicenter, randomized, double-blind, parallel-controlled clinical trial intended to assess the safety and efficacy of a combined CRT-ICD system in patients with dilated cardiomyopathy (left ventricular ejection fraction ≤35%, left ventricular end diastolic dimension ≥55 mm), NYHA class III or IV HF, ventricular dyssynchrony (QRS ≥ 130 msec), and an indication for an ICD. Primary and secondary efficacy measures were essentially the same as those that were evaluated in the MIRACLE trial, but also included measures of ICD function (including the efficacy of antitachycardia therapy with biventricular pacing).

Of 369 patients receiving devices and randomized, 182 were controls (ICD active, CRT inactive) and 187 were in the resynchronization group (ICD active, CRT active). At 6 months, patients assigned to active CRT had a greater improvement in median quality-of-life score (–17.5 versus –11.0, P = 0.02) and functional class (–1 versus 0, P = 0.007) than controls, but were no different than controls in the change in distance walked in 6 minutes (55 m versus 53 m, P = 0.36).[38] Peak oxygen consumption increased by

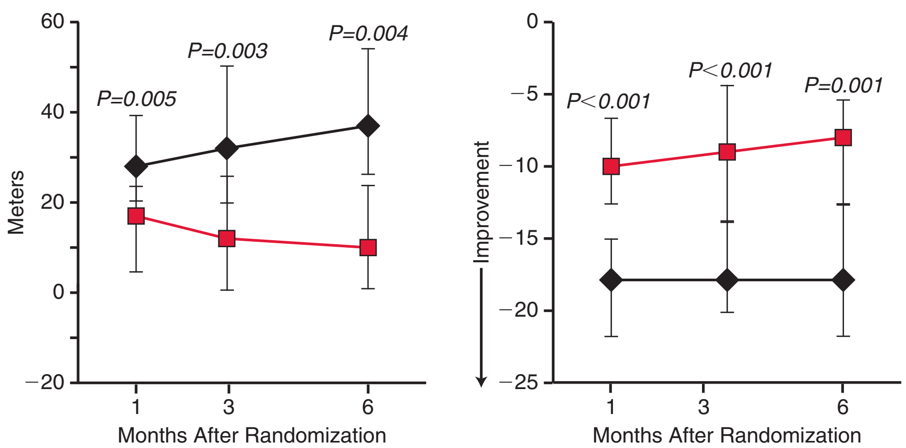


Figure 15–2 Effect of cardiac resynchronization therapy on 6-minute hall walk distance (*left panel*) and quality-of-life score (*right panel*) in the MIRACLE trial. Shown are median changes (and their respective 95% confidence intervals) at 1, 3, and 6 months after randomization in the control (*closed squares*) and the cardiac resynchronization groups (*closed diamonds*). A reduction in quality-of-life score denotes improvement. P values denote significant between-group differences. For each variable, data are shown for patients who had values at all three time points.

1.1 mL/kg/min in the resynchronization group, versus 0.1 mL/kg/min in controls ($P = 0.04$) and treadmill exercise duration increased by 56 seconds in the CRT group and decreased by 11 seconds in controls ($P = 0.0006$). The magnitude of improvement was comparable with that seen in the MIRACLE trial, suggesting that HF patients with an ICD indication benefit as much from cardiac resynchronization therapy as those patients without an indication for an ICD. The combined CRT-ICD device used in this study was approved in June 2002 by the FDA for use in NYHA classes III and IV systolic HF patients with ventricular dyssynchrony and an ICD indication.

CONTAK CD

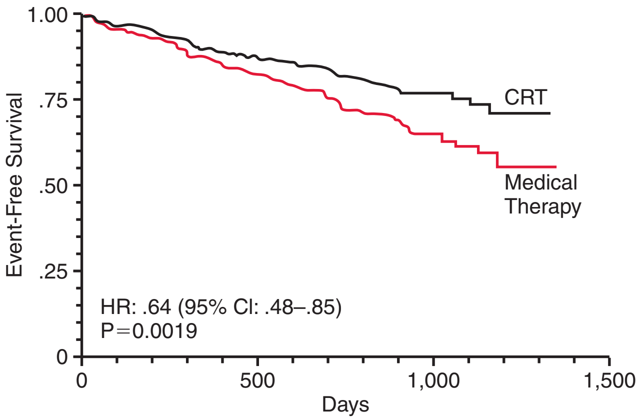
The CONTAK CD trial enrolled 581 symptomatic HF patients with ventricular dyssynchrony and malignant ventricular tachyarrhythmias, all of whom were candidates for an ICD.[39] Following unsuccessful implant attempts and withdrawals, 490 patients were available for analysis. The study did not meet its primary endpoint of a reduction in disease progression, defined by a composite endpoint of HF hospitalization, all-cause mortality, and ventricular arrhythmia requiring defibrillator therapies, although the trends were in a direction favoring improved outcomes with CRT. However, the CONTAK CD trial did show statistically significant improvements in peak oxygen uptake and quality of life in the resynchronization group compared with control subjects, although quality of life was improved only in NYHA classes III and IV patients without right bundle branch block. Left ventricular dimensions were also reduced and left ventricular ejection fractions increased—as seen in other trials of CRT. Importantly, the improvement seen in peak oxygen consumption with cardiac resynchronization was again comparable with that observed in the MIRACLE trial. Improvements in NYHA functional class were not observed in this study. The CONTAK CD device was approved in May 2002 by the FDA for use in NYHA classes III and IV systolic HF patients with ventricular dyssynchrony and an ICD indication.

COMPANION

Begun in early 2000, COMPANION was a multicenter, prospective, randomized, controlled clinical trial designed to compare drug therapy alone with drug therapy in combination with cardiac resynchronization in patients with dilated cardiomyopathy, an IVCD, NYHA class III or IV HF, and no indication for a device.[43,44] COMPANION randomized 1520 patients into one of three treatment groups in a 1:2:2 allocation: Group 1 (308 patients) received optimal medical care only, group II (617 patients) received optimal medical care and the Guidant CONTAK TR (biventricular pulse generator), and group III (595 patients) received optimal medical care and the CONTAK CD (combined HF/bradycardia/tachycardia device). The primary endpoint of the COMPANION trial was a composite of all-cause mortality and all-cause hospitalization, measured as time to first event, beginning from time of randomization. Secondary endpoints included all-cause mortality and a variety of measures of cardiovascular morbidity. When compared with optimal medical therapy alone, the combined endpoint of mortality or HF hospitalization was reduced by 35% for patients receiving CRT and by 40% for patients receiving CRT-ICD (both $P < 0.001$). For the mortality endpoint alone, CRT patients had a 24% risk reduction ($P = 0.060$) and CRT-ICD patients experienced a risk reduction of 36% ($P < 0.003$), when compared with optimal medical therapy. COMPANION confirmed the results of earlier resynchronization therapy trials in improving symptoms, exercise tolerance, and quality of life for HF patients with ventricular dyssynchrony. In addition, COMPANION showed—for the first time—the impact of CRT-ICD in reducing all-cause mortality.

CARE-HF

The Cardiac Resynchronization-Heart Failure (CARE-HF) trial was designed to evaluate the effects of resynchronization therapy without an ICD on morbidity and mortality rates in patients with NYHA class III or IV HF and ventricular dyssynchrony.[40,41] Patients ($N = 813$) with an LV ejection fraction of 35% or less and ventricular dyssynchrony defined as a QRS duration ≥150 msec or a QRS duration between 120 msec and 150 msec with echocardiographic evidence of dyssynchrony were enrolled in this randomized, unblinded, controlled trial and followed for an average of 29 months.[41] Optimal medical therapy alone was assigned to 404 patients and 409 patients were randomized to optimal medical therapy plus resynchronization therapy. The risk of death from any cause or unplanned hospitalization for a major cardiac event, the primary endpoint analyzed as time to first event, was significantly reduced by 37% in the treatment group compared with control subjects (hazard ratio, 0.63; 95% CI, 0.51 to 0.77; $P < 0.001$). In the CRT group, 82 patients (20%) died during follow-up compared with 120 patients (30%) in the medical group, yielding a significant 36% reduction in all-cause mortality with resynchronization therapy (hazard ratio, 0.64; 95% CI, 0.48 to 0.85; $P < 0.002$; Fig. 15–3). Resynchronization therapy also significantly reduced the risk of unplanned hospitalization for a major cardiac event by 39%, all-cause mortality plus HF hospitalization by 46%, and HF hospitalization by 52%.



Number at risk

CRT	409	376	351	213	89	8
Medical Therapy	404	365	321	192	71	5

Figure 15–3 Kaplan-Meier estimates of survival in patients randomized to CRT compared with conventional medical therapy in the CARE-HF trial.

INDICATIONS FOR CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE PATIENTS

The 2005 ACC/AHA HF guidelines propose a class I indication for CRT.[1] Patients with a left ventricular ejection fraction of ≤35%, normal sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms, despite recommended optimal medical therapy, and who have ventricular dyssynchrony should receive CRT, unless contraindicated. Currently, the guideline defines ventricular dyssynchrony as a QRS duration of at least 120 msec. However, echocardiography appears to be a promising way to define ventricular dyssynchrony in the future, so a newer definition of ventricular dyssynchrony may eventually prevail.

FUTURE DIRECTIONS OF CARDIAC RESYNCHRONIZATION THERAPY

There are several unresolved issues related to cardiac resynchronization therapy in HF. Despite the widespread use of CRT, further advances in device and lead technology are needed. In up to 10% of patients, percutaneous LV lead placement cannot be performed because of failure of cardiac vein cannulation. Additionally, implant procedures may be complicated by coronary sinus dissection, and late lead malfunction or dislodgment may occur. Select patients are referred for surgical epicardial LV lead placement, but outcomes are not well described. Newer lead systems and minimally invasive surgical procedures are under development and randomized studies will be needed to determine the safety and efficacy of these new techniques.

Although current guidelines recommend CRT for a broad range of patients with moderate-to-severe HF and reduced ejection fraction, there remain several HF populations in whom the benefits of CRT remain unclear. Data from the MIRACLE ICD II study showed that patients with NYHA class II HF and an indication for an ICD experienced reverse ventricular remodeling with CRT, but functional benefits were less clear.[45] The role of CRT in patients with asymptomatic LV dysfunction, as well as those with mild HF, is currently being tested in randomized controlled trials. Smaller studies also suggest a benefit of CRT in patients with atrial fibrillation or after upgrade from right ventricular to biventricular pacing, but more data are needed before strong recommendations can be made. Studies are also in progress to determine the role of CRT in patients with normal QRS duration, but with ventricular dyssynchrony documented by echocardiography. At present, CRT is not recommended for patients with unstable or refractory HF. Further investigations are needed to identify those variables that predict structural and functional responses to CRT.[46]

MONITORING HEART FAILURE THROUGH IMPLANTABLE DEVICES

Either as stand-alone devices or combined with CRT and ICD devices, implantable monitoring technologies are rapidly being applied to the management of HF. Implantable devices can provide a wealth of physiologic information about the clinical status of HF patients, and the use of this information may improve HF outcomes. For example, many implantable CRT and ICD devices can provide information on atrial heart rate and rhythm, ventricular heart rate and rhythm, patient activity level, and heart rate variability (HRV), and an increasing number of FDA-approved implantable CRT-ICD devices can also track changes in intrathoracic impedance. By monitoring trends in such parameters, it may be possible to predict episodes of worsening HF.

HF patients are encouraged to remain active and to engage in regular physical exercise, such as walking. The activity trend recorded by many implantable devices provides an objective record of the number of hours per day that patients are physically active. Thus, the activity report can serve as a useful teaching and reinforcement tool for both the patient and family about the importance and level of activity. Because exercise intolerance is a hallmark of worsening HF, a decrease in measured patient activity level may provide one clue to disease progression or decompensation. This measurement may be viewed as complementary to the patient history and, perhaps, as more objective. The predictive value of objectively measured changes in patient activity level is currently under investigation. To date, anecdotal reports suggest that a reduction in measured patient activity level precedes overt HF decompensation.

Adamson and associates[47] evaluated the usefulness of following changes in HRV as a marker of HF clinical status. HRV reflects the balance between sympathetic and parasympathetic nervous system activity in the heart, with a decrease in HRV serving as a sign of increased sympathetic and decreased parasympathetic tone.[48] This analysis showed that HRV diminished in the days to weeks leading up to a hospitalization for worsening HF, thereby suggesting that decreases in HRV can predict HF decompensation.[47] The notion that changes in continuously monitored HRV may be predictive of worsening HF is attractive because it fits well with our understanding of the mechanisms leading to worsening HF or HF disease progression—specifically activation of the sympathetic nervous system.

The ability of implantable devices to monitor fluid status is currently based on monitoring changes in intrathoracic impedance. Electrical impedance can be determined between the generator and the ICD lead residing within the right ventricle. Essentially, electrical impedance is measured across the lung, from the tip of the lead to the generator (Fig. 15–4). Because water conducts electricity better than air, increasing lung water is associated with a decrease in electrical impedance. Using this technique, electrical impedance is assessed multiple times throughout the day and then plotted on a graph. The fluid volume thresholds can be adjusted by the clinician based on patient symptoms and reviewed to determine volume status. Clinical evaluation of intrathoracic impedance changes has shown its ability to predict hospitalizations for decompensated HF 10 to 14 days in advance of the event.[49] The challenge for clinicians is knowing how to react to this information, especially in the absence of signs or symptoms of congestion. Further evaluation of intrathoracic fluid monitoring and its effects on HF outcomes is under investigation.

A new generation of even more sophisticated implantable monitoring devices is under investigation. These devices allow continuous or intermittent assessment of hemodynamics,

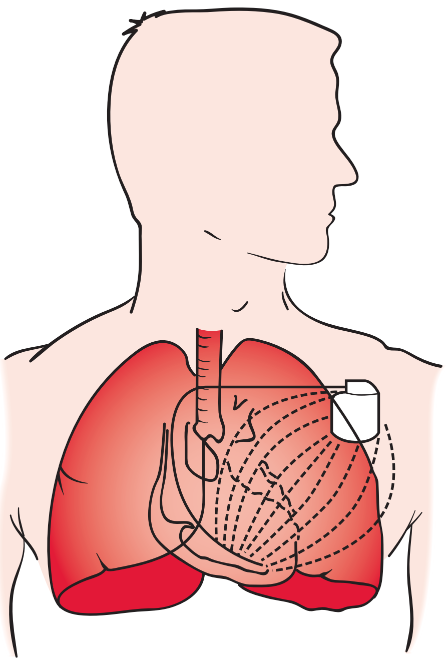


Figure 15–4 Diagram depicting the concept underlying intrathoracic impedance monitoring in heart failure. An electrical current is passed from the tip of the right ventricular lead to the "can" (i.e., generator). The impedance to the flow of electricity through the lung can be measured. Increased lung water is associated with a decrease in impedance, whereas a decrease in lung water is seen as an increase in intrathoracic impedance.

generally focused on the direct measurement or estimation of left-sided filling pressure. One of these implantable hemodynamic monitoring systems has undergone extensive evaluation in clinical trials; it has been shown to be safe, to provide an accurate estimate of left ventricular filling pressure, and to reduce the number of worsening HF events.[50-52] This system enables the continuous assessment of hemodynamics and provides this information to the clinician via a secure web site. Other systems empower patients to self-manage left ventricular filling pressure in the same way that diabetics self-manage glucose levels through the use of a glucometer. The potential for these devices to revolutionize the management of HF is substantial but remains under investigation.

FUTURE DIRECTIONS IN IMPLANTABLE DEVICES FOR THE MANAGEMENT OF HEART FAILURE

A variety of other implantable devices are under evaluation for the management of HF. In many ways, we are now in a "device era" for the management of the disease. One promising approach is cardiac contractility modulation or CCM.[53] This implantable device delivers an intermittent electrical impulse to the heart during the absolute refractory period of the ventricle. Although the mechanism of action of this investigational therapy is incompletely understood, it may be thought of as a form of electrical conditioning of the heart whereby electrically mediated changes in myocyte calcium handling improve contractility. This improvement in contractility occurs in association with a reduction in myocardial oxygen consumption, suggesting improved efficiency of the heart.[54] This favorable relationship between myocardial contractility and work has been associated with improved outcomes for other HF therapies, such as CRT. A large-scale randomized controlled trial of CCM is underway. Other implantable HF devices are in preclinical and early clinical evaluations.

SUMMARY

Cardiac resynchronization therapy offers a new therapeutic approach for treating patients with ventricular dyssynchrony and moderate-to-severe HF. Substantial experience suggests that it is safe and effective—with patients showing significant improvement in clinical symptoms and multiple measures of functional status, exercise capacity, and outcomes. The beneficial effects of CRT on ventricular structure and function have also been demonstrated in multiple clinical studies. Prophylactic implantation of an ICD is also now of proven benefit in HF patients, at least in those with NYHA classes II and III disease. Implantable monitoring technologies promise to improve our ability to avoid episodes of HF decompensation and may improve the natural history of the disease. Other investigational devices may add incremental benefit to the treatment of HF.

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Chapter 16

Surgical Treatment of Heart Failure

Eric J. Velazquez

CHAPTER CONTENTS

Marked increases in the incidence and prevalence of heart failure (HF) have been observed over the last several decades.[1] This epidemiologic trend is attributed to a combination of an aging population, declining mortality associated with ischemic heart disease and hypertension (the most common causes of HF), and major therapeutic advances in the treatment of left ventricular systolic dysfunction (LVSD). Current estimates are that HF affects more than 5 million patients in the United States and is directly responsible for 1 million hospitalizations and 570,000 deaths annually with an estimated cost to society exceeding $29 billion.[2,3]

Cardiac surgical approaches to the diseased left ventricle have matured in the setting of this changing HF environment. Cardiac surgery represents one of the keystone developments in the practice of cardiovascular medicine. This chapter focuses on the current surgical approaches to the management of HF and LVSD in adults. Because they represent the most common considerations in HF patients, coronary artery bypass graft surgery, ventricular reconstruction procedures, and operative procedures to reduce mitral regurgitation are reviewed in depth as to their developmental history, current role in HF management, selection criteria, and operative considerations and outcomes. Timing of, and techniques for, surgical management of other valvular disorders, including aortic stenosis, aortic regurgitation, and tricuspid regurgitation, in the setting of HF are detailed in Chapters 46 and 47 and other reviews.[4] Some attention is given here to experimental approaches evaluated and likely to be adopted into limited clinical use. A discussion of surgically-based cellular and gene therapies for HF[5] is beyond the scope of this chapter.

Although cardiac surgery for HF has advanced greatly since the 1960s, many unanswered questions remain; these are addressed along with a brief overview of the status of ongoing clinical investigations.

CORONARY ARTERY BYPASS SURGERY

Shortly after Favaloro's description of aortocoronary saphenous vein bypass surgery,[6] initial reports followed of its application to patients with HF.[6] Although conflicting conclusions were drawn, the 30-day mortality rates of 15% and 25% in those surgical series were sobering.[7,8] Further dampening any early enthusiasm, the initial cohort studies comparing cardiac surgery with medical approaches in patients with ischemic cardiomyopathy suggested that coronary surgery led to no incremental relative improvement in either short- or longer-term symptoms or survival.[9] The high operative rates led many to consider LVSD to be a contraindication to coronary surgery and limited its initial widespread use in patients with HF.

Early efforts at medical therapy alone for ischemic cardiomyopathy probably did not alter the natural history of HF because treatment was limited to bed rest, digitalis, nitrates, and diuretics and was universally associated with poor long-term survival.[10,11] Notwithstanding the high operative mortality initially reported, the long-term mortality afforded by medical approaches alone was dismal and led to continuing efforts to expand cardiac surgery to patients with coronary artery disease, HF, and LVSD. The growing experience and continuing refinement of coronary artery bypass graft surgery (CABG) led to several case series, which suggested that surgical revascularization with or without left ventricular aneurysmectomy for patients with a left ventricular ejection fraction (EF) below 40% could be accomplished with acceptable operative mortality for that era (0% to 30%) and lead to improvements in functional status.[12-14] Furthermore, some single-center case series began reporting that surgical approaches to obstructive coronary disease with angina, HF, and LVSD could enhance 2-year survival and freedom from angina and HF compared with medical therapy.[15] Manley and colleagues also reported that, in patients presenting with angina, those treated surgically derived a long-term (6 year) survival advantage (60% versus 40%) when compared with a contemporary medically treated cohort.[16]

While operative outcomes were improving through this initial decade of coronary artery surgery, patients with severe impairments of left ventricular function remained at such high operative risk that they were excluded from the three large randomized clinical trials of coronary artery surgery or medical therapy for the treatment of chronic stable angina. Of the 2234 patients enrolled in the three landmark clinical trials between 1971 and 1979,[17-19] none had severe LVSD. Only the Coronary Artery Surgery Study (CASS) enrolled patients with any impairment of left ventricular function (EF 35% to 50%). The cohort with modest ventricular dysfunction randomized into CASS included 78 patients who underwent coronary artery surgery among whom 11 deaths occurred and 82 medically treated patients among whom 25 deaths occurred.[20] Although the survival of patients with single- and two-vessel

disease was similar among the treatments, of the 78 patients with three-vessel disease, those treated surgically instead of medically had improved survival at 7 years.

A meta-analysis by Yusuf and colleagues[22] combined individual patient data from the CASS trial with those patients enrolled in all six of the early-randomized trials of coronary surgery. Only 191 (7.2%) of the 2649 total patients enrolled had an EF less than 40%, and only 106 (4.0%) of these patients, who were primarily symptomatic with angina, also had HF symptoms. The CABG Trialists group suggested that coronary surgery led to improved survival among all patients with proximal left anterior descending artery disease, three-vessel disease, or left main coronary artery disease regardless of left ventricular function. In this analysis, a low EF increased the absolute benefit but did not change the relative benefit of coronary artery surgery. Furthermore, a 1994 literature search of 326 published reports on the results of coronary artery surgery in patients with HF or LVSD identified only three well-designed cohort studies. The mortality benefit of coronary artery surgery beyond medical therapy was estimated to be 10 to 29 lives per 100 patients treated.[23]

Patients screened for CASS with severe LVSD (EF 35% or less and poor wall motion score) not eligible for randomization were enrolled in a registry.[21] Of these 751 CASS registry patients, 231 were treated surgically and 420 were treated medically. The overall 5-year survival favored medical therapy (32% versus 46%), but only in the subset of patients (82 undergoing coronary artery surgery, 172 medically treated) with an EF less than 26% was a statistical advantage demonstrated for surgical revascularization ($P = 0.006$). In the CASS registry, the surgically treated group had more severe angina and severe coronary artery disease (66.7% with three-vessel disease and 12.6% with left main lesions >70%) in the setting of less left ventricular dysfunction and symptoms of heart failure. When the groups were evaluated by the predominance of either angina or HF symptoms, the patients with angina who were treated surgically manifested improved survival free of major functional limitation, whereas those patients with HF (11.1% surgically treated and 18.8% medically treated) did not. These data led the CASS registry investigators in 1983 to summarize their results for patients with severe LVSD by suggesting that "patients with overt heart failure and the absence of ischemic symptoms should not receive surgery." This perspective influenced treatment decisions for the next 2 decades and was cited as late as 2001 in the ACC/AHA HF Guidelines, which gave coronary revascularization for patients with HF in the absence of angina a class IIb recommendation.[24]

Since CASS there have been a multitude of single-center small case series and larger observational studies[25-31] reporting patient outcomes with coronary artery surgery in HF with LVSD. The Duke Databank experience published in 2002 is the largest of these studies and summarized the comparative results on long-term morbidity and mortality outcomes of 339 patients who received CABG and 1052 patients who were continued on medical therapy with the diagnosis of HF and an EF less than 40% and who underwent cardiac catheterization from 1969 to 1994.[32] After adjustment for differences in baseline characteristics between the groups, CABG was strongly associated with better event-free and overall survival—regardless of the extent or severity of coronary artery disease, heart failure symptoms, or LVSD. Importantly, unlike in the CASS registry, the presence of angina did not appear to discriminate patients who had a good outcome with surgery (Figs. 16–1 and 16–2).

Increasing numbers of high-risk patients, such as those with HF and LVSD, are currently referred for coronary artery surgery.[33] Fortunately, contemporary national database analyses reveal a corresponding significant decline in risk-adjusted mortality rates.[34] Technical improvements, such as the near universal use of internal mammary artery conduits, modifications to cardiopulmonary bypass and myocardial protection techniques, along with improved surgical skill and cardiac anesthesia care, have undoubtedly contributed to the greater number of high-risk patients now undergoing surgery and the better outcomes.

Topkara and colleagues analyzed 55,515 patients who underwent coronary surgery between 1997 and 1999 from the New York State database and found that LVSD was highly prevalent among patients referred for CABG, with over 35% presenting with an EF less than 40%.[35] In 14.8% of the patients, the EF was 30% or less. Patients with the lower EFs had a significantly higher in-hospital mortality rate after coronary surgery (6.5% for EF <20%, 4.1% for EF 21% to 30%, 2.7% for 31% to 40%) when compared with those patients with more preserved left ventricular function (1.4% for EF > 40%). In the lowest EF group, increasing age, female gender, hepatic insufficiency, renal failure, HF symptoms, procedural urgency, acute myocardial infarction, and previous cardiac surgery were significant predictors of a poor outcome.

Patient selection remains an important factor in achieving favorable outcomes after CABG, especially among those with HF and LVSD, and has been extensively evaluated.[36] Cardiac catheterization is mandatory to define native, and in the case of reoperation CABG, graft anatomy as well as suitability of distal vessel targets (see Chapter 8). In addition, important hemodynamic data including presence and reversibility of pulmonary hypertension and evidence of right ventricular failure assist in risk stratification and perioperative management. Careful search for end-organ dysfunction, including secondary renal and hepatic impairment, and concomitant pulmonary and peripheral arterial disease, is also necessary to assess and minimize surgical risk. One explicit goal of coronary surgery selection paradigms is to maximize the likelihood of improved functional status and survival at the lowest risk. The potential reversibility of LVSD in patients with myocardial viability has been likened by some to the holy grail of coronary surgery in HF, and it is estimated that up to 40% of patients with coronary artery disease may have the potential for improved left ventricular function after coronary surgery.[27,37]

Viability testing by various modalities is currently used by many clinicians to select appropriate patients for coronary surgery.[37-39] Positron emission tomography (PET) is considered by many to be the standard for assessing the presence and extent of hibernating myocardium.[37] Severely hypokinetic or akinetic regions that demonstrate decreased or absent perfusion in the presence of normal metabolism (assessed by ^{18}F-deoxyglucose (FDG) uptake)—also referred to as *flow-metabolism mismatch* are likely to recover function after revascularization.[40] Unfortunately, lack of availability, requirement for on-site production of isotopes, and high costs have limited the widespread use of PET imaging. An older and more readily available nuclear cardiology test is thallium-201 scintigraphy with rest and redistribution or reinjection

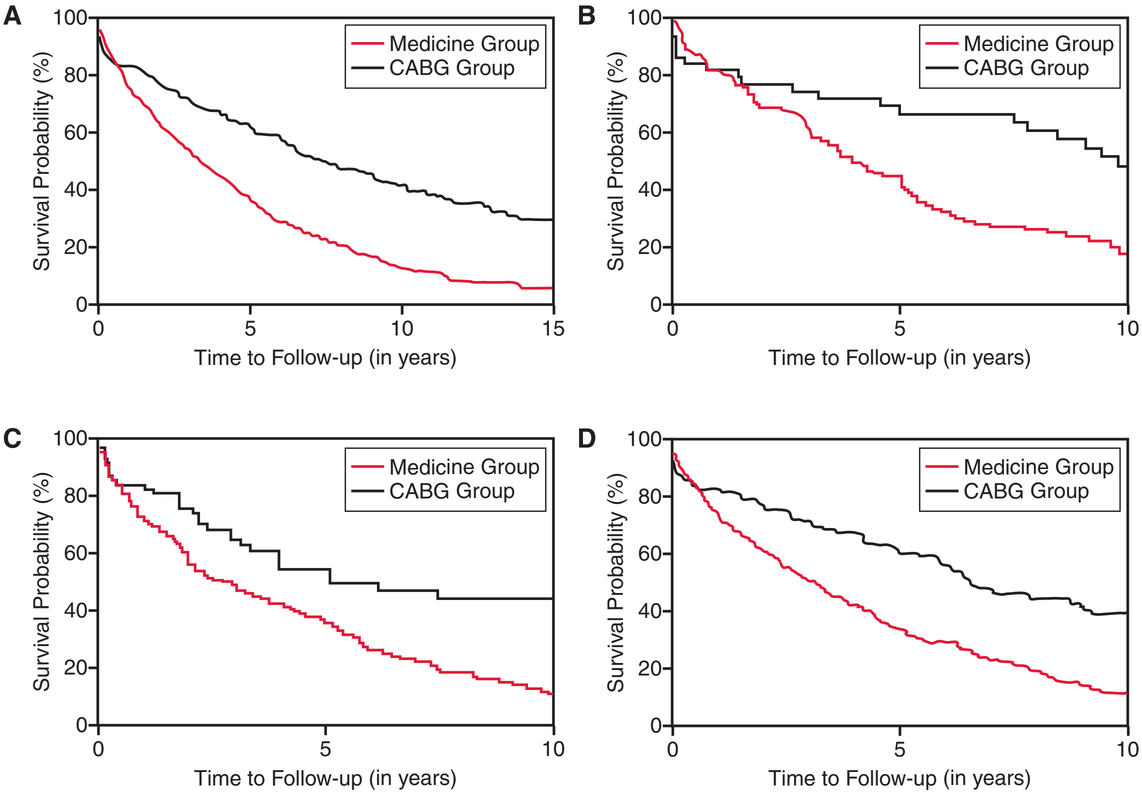

Figure 16–1 A 25-year experience from the Duke Cardiovascular Disease Databank. Adjusted survival curves for CABG versus medical therapy. **A,** overall; **B,** one-vessel disease; **C,** two-vessel disease; **D,** three-vessel disease. (Adapted from O'Connor CM, Velazquez EJ, Gardner LH, et al: Comparison of coronary artery bypass grafting versus medical therapy on long-term outcome in patients with ischemic cardiomyopathy: A 25-year experience from the Duke Cardiovascular Disease Databank. Am J Cardiol 2002;90:101-7, reproduced with permission.)

imaging. However, compared with PET, thallium viability testing has lower specificity, may overestimate potential improvement in EF, and is more time consuming. Given its relatively low cost and widespread availability, low-dose dobutamine stress echocardiography is the viability test of choice at many institutions. This test is based on the concept that hibernating myocardium is able to demonstrate an augmented contractile response to β-adrenergic stimulation. The addition of myocardial strain analysis may further enhance the sensitivity of this technique for viability assessment,[41] while β-receptor hypo-responsiveness and ischemia may cause false negatives. For patients without pacemakers or implantable cardioverter-defibrillators, cardiac magnetic resonance imaging is an alternative to PET for assessing viability with high sensitivity and specificity.[39] Gadolinium imaging is used to identify areas of delayed hyper-enhancement that are unlikely to recover function with surgical revascularization.

The presence of viability in patients with LVSD and coronary disease appears to predict recovery of contractile function, regardless of whether patients receive medical therapy alone or CABG.[42,43] Many retrospective, nonrandomized observational series of the association of viability testing and differential outcomes with CABG and medical therapy for ischemic cardiomyopathy have been published, with results summarized in several recent meta-analyses.[44,45] A clinical algorithm has been proposed integrating viability testing into the diagnostic and therapeutic approaches to patients with

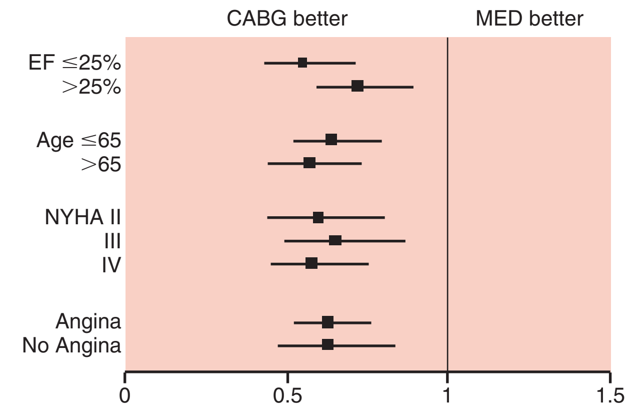

Figure 16–2 A 25-year experience from the Duke Cardiovascular Disease Databank.[32] Hazard ratios (95% confidence interval) for mortality in subgroups defined by baseline characteristics. CABG, coronary artery bypass graft surgery; EF, ejection fraction; MED, medical; NYHA, New York Heart Association. (Adapted from O'Connor CM, Velazquez EJ, Gardner LH, et al: Comparison of coronary artery bypass grafting versus medical therapy on long-term outcome in patients with ischemic cardiomyopathy: A 25-year experience from the Duke Cardiovascular Disease Databank. Am J Cardiol 2002;90:101-7, reproduced with permission.)

LVSD[46] (Fig. 16–3). Although the published data, including an analysis from the Cleveland Clinic Foundation,[40] suggest that patients with coronary disease, LVSD, and viable myocardium who are eligible for revascularization may have improved short- and long-term outcomes with coronary surgery, a multitude of confounding factors limits the applicability of the data to current HF patients. In particular, additional procedures performed at the time of CABG including mitral and/or tricuspid valve repair, transmyocardial laser revascularization,[47] or placement of an epicardial left ventricular lead for cardiac resynchronization therapy[48] may significantly affect postoperative results. Nonetheless, it is unlikely that any effect of CABG over medical therapy in patients with LVSD depends solely on the presence of viability or the likelihood of functional recovery.[49]

Advances in percutaneous coronary interventions (PCI) are also likely contributing to the increasing prevalence of high-risk patients referred to coronary surgery, as lesser risk anatomic substrates and patient subsets are preferentially referred to nonsurgical revascularization. As PCI procedural techniques continue to improve, there has been growing interest among interventional cardiologists in tackling higher risk patients. Nonetheless, in the PCI era there is a paucity of studies evaluating revascularization for HF and low EF. The Bypass Angioplasty Revascularization Investigation compared balloon angioplasty with coronary surgery among patients enrolled from 1989 to 1992 with coronary anatomy deemed approachable by either revascularization approach. Although very few patients had HF or an EF less than 50%, HF was one of the most powerful predictors of mortality in both the surgical and medical groups.[50] The VA AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial and registry experience evaluated percutaneous and surgical revascularization among 2431 patients with medically refractory ischemic coronary disease and high operative risk of whom approximately 20% had an EF of 35% or less and

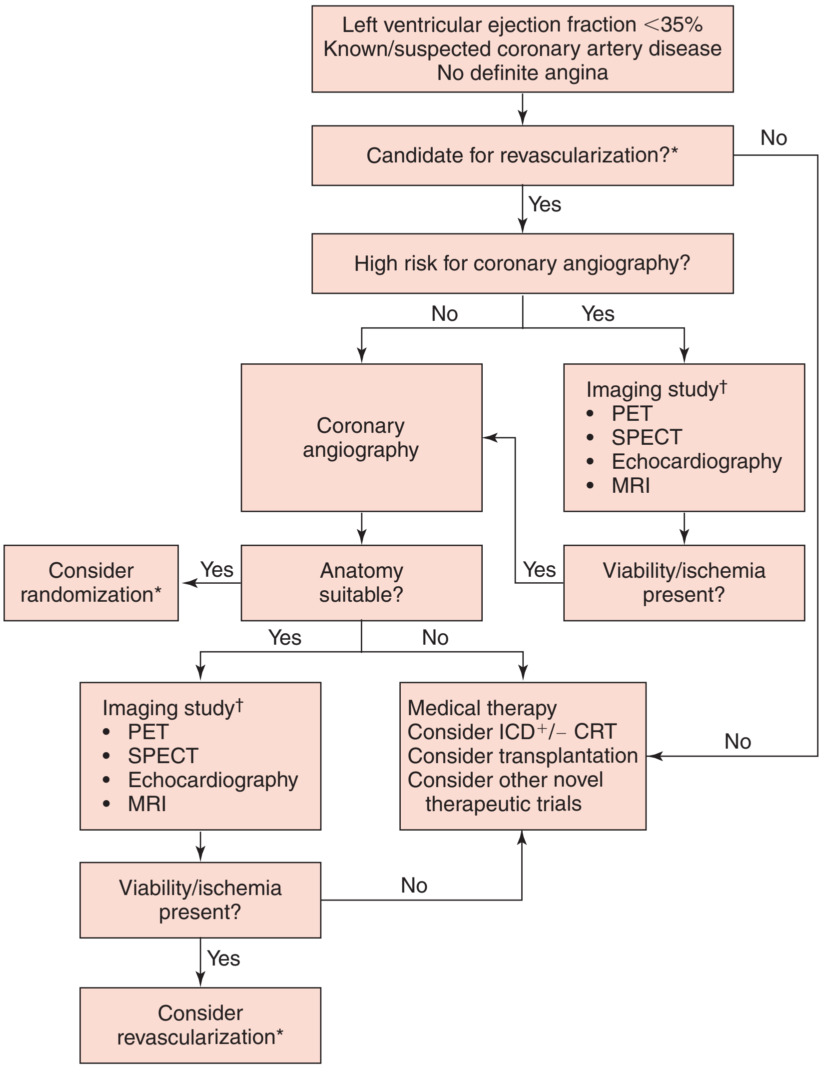

Figure 16–3 Algorithm of proposed clinical approach to revascularization in ischemic cardiomyopathy integrating diagnostic and therapeutic decisions. ICD, implantable cardioverter-defibrillator; MRI, magnetic resonance imaging; PET, positron-emission tomography; SPECT, single photon-emission computerized tomography. (Adapted from Chareonthaitawee P, Gersh BJ, Araoz PA, et al: Revascularization in severe left ventricular dysfunction. J Am Coll Cardiol 2005;46:567-74, reproduced with permission.)

found comparable morbidity and mortality rates.[51] In contrast to the VA AWESOME results, Hannan and coworkers[52] reported on the results of 37,212 patients who received coronary surgery and 22,102 patients who underwent a PCI with stents for multivessel coronary disease. Patients with an EF of 40% or less were proportionally more common among those receiving coronary surgery compared with PCI (25.9% versus 18.5%). Coronary surgery was associated with better adjusted long-term outcomes when compared with PCI for patients with LVSD with two-vessel disease and proximal left anterior artery lesions and for three-vessel disease. When comparing coronary surgery with PCI in patients with multivessel disease, complete revascularization is more frequently achieved by coronary surgery and likely relates to the higher rates of repeat revascularization found among those receiving PCI.[53] The impact on short- and long-term outcomes of incomplete revascularization and/or repeat revascularization among low EF patients has not been well studied but likely further differentiates PCI and coronary surgery in HF. Because the current state of the evidence for PCI in low EF patients does not support widespread adoption, the proportion of patients with HF and LVSD referred to CABG is anticipated to climb in the near future.

CABG has evolved within a changing environment of heart disease[54] (Fig. 16–4). Over the last 35 years, coronary surgery for patients with HF and LVSD has gone from contraindicated to conventional. Advancements in the use of arterial conduits and endarterectomy, improved techniques for myocardial protection and reduction of stroke risk, success with reoperation CABG, and emerging experience with off-pump surgery have all contributed to improved surgical outcomes.[48a] It is also important to recognize that nonsurgical approaches for HF have undergone equally remarkable advances.[55] For example, patients randomized to medical therapy in CASS did not systematically receive any of the evidence-based therapies that are now reported cardiac care quality indicators, including aspirin, statins, angiotensin-converting enzyme inhibitors, and β-blockers. Furthermore, none of the current adjunctive pharmacologic and device therapies to reduce morbidity and mortality in HF was available. The impact of an EF less than 35% and/or moderate-to-severe HF on long-term survival in CASS was sobering—with a 12-year survival rate of approximately 10%.[56] Today, clinical trials in similar patient subsets report 80% survival at 2 to 3 years.[57] As nonsurgical therapy advances, it will be critically important to understand whether CABG adds any incremental benefit beyond the optimal medical therapy and whether certain patient subsets are at risk for worse outcomes without CABG. The National Heart, Lung and Blood Institute (NHLBI)-funded STICH (Surgical Treatment for Ischemic Heart Failure) trial (*www.stichtrial.org*) promises to address this and many other questions regarding coronary surgery for HF (Fig. 16–5).[58]

SURGICAL VENTRICULAR RESTORATION

In some of the earliest series of coronary artery surgery for HF, the operation was combined with myocardial resection of asynergic predominantly anterior or apical ventricular segments.[59] As early as 1969 and on the understanding of the Frank-Starling mechanism and the Laplace relationship, modification of ventricular asynergy was considered a theoretically attractive potential treatment for HF.[60] The recognition of the important association between ventricular dilatation and HF symptom severity and outcomes[61] fueled the hopes that surgical removal of akinetic, dyskinetic, or aneurysmal segments would (1) reduce wall tension, myocardial oxygen consumption, and the sequestration of stroke volume; and (2) increase contractile function in the remaining ventricle with and without concomitant coronary artery surgery.[62-65] The recognition that ventricular asynergy could result from chronic ischemia without infarction and that coronary artery bypass surgery alone could lead to improvements in hemodynamics, ejection fractions, and ventricular volumes in patients with and without previous infarction

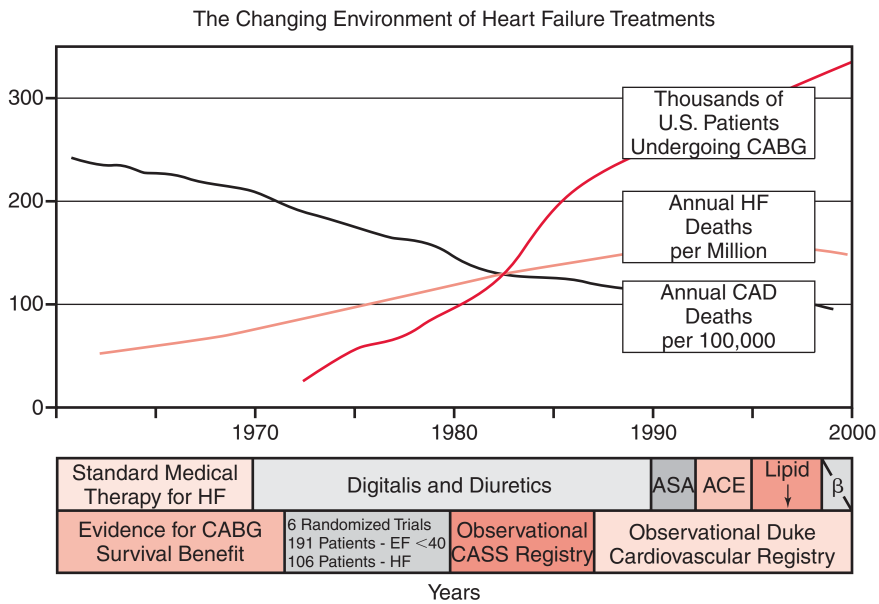

Figure 16–4 The changing environment of coronary surgery and heart failure treatment. (Adapted from Barker WH, Mullooly JP, Getchell W: Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation 2006;113:799-805; Jones R: The year in cardiovascular surgery. J Am Coll Cardiol 2005;45:1517-28; and Kaessmeyer Circulation 1994;90:1029-32 and AHA 2001 Statistical Update.)

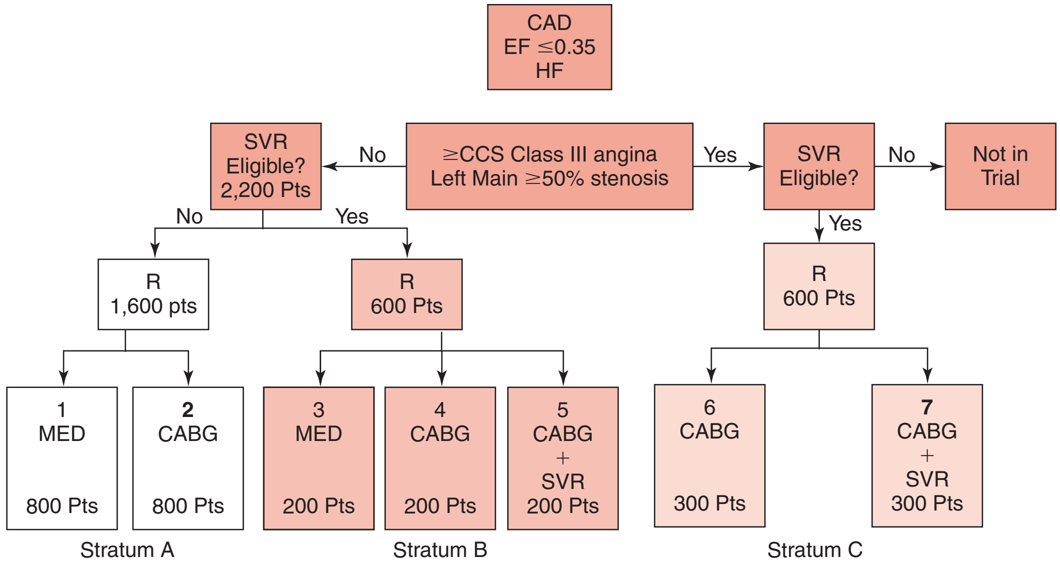

Figure 16–5 Algorithm of randomization scheme for the Surgical Treatment in Ischemic Heart Failure (STICH) trial. CABG, coronary artery bypass graft surgery; CCS, Canadian Cardiovascular Society; EF, ejection fraction; HF, heart failure; MED, medical treatment; SVR, surgical ventricular restoration.

began a debate still raging today regarding the role of myocardial resection as a treatment for HF.[66]

Left ventricular aneurysmectomy as first described by Cooley in 1958[67] appeared to reverse HF by lowering left ventricular wall stress, but this linear amputation of dyskinetic scar commonly deformed the LV cavity into a box-like shape and did not improve left ventricular performance.[68] Intracavitary reconstruction techniques have been developed for repairing defects left by aneurysm resection that reduced LV cavity size.[69,70] The general reconstruction technique (Fig. 16–6) uses an endoventricular circular continuous suture to exclude dysfunctional septal and apical regions and has evolved with multiple variations, such as direct closure versus patch plasty with or without myocardial resection. Several sizing balloons and devices are now used to define optimal volume reduction. A more detailed description of the surgical technique is available elsewhere.[71] This surgical ventricular restoration (SVR) strategy as initially popularized by Dor[70] has been applied not only to patients with dyskinetic scar but also to those with only akinetic myocardial segments. At the time of cardiac operation, the epicardium of these akinetic zones may appear normal, and palpable thinning is often minimal in the arrested, decompressed heart. This appearance derives from preservation of a rim of normal myocardium covering the myocardial fibrosis and contrasts with the leather-like appearance and thinness typical of a left ventricular aneurysm.

Unlike the LV aneurysmectomy that removed myocardial scar or the Batista operation[72] that reduced left ventricular size by removal of portions of the wall, the SVR operation mechanically decreases the circumference of the zone of endocardial scar through an incision in normal epicardium. The surgical repair uses the intrinsic scar or an extrinsic patch to absorb excess linear wall tension from the adjacent myocardium. A decrease in wall stress appears to reduce the tendency for continued gradual expansion of the akinetic zone. The endocardial repair acutely decreases ventricular size and mitral regurgitation; this surgical remodeling acutely enhances function in myocardial regions remote from the repair and improves forward stroke volume.

Dor and colleagues, along with other groups, have reported favorable short-term hemodynamic results and long-term results with SVR in patients with ischemic cardiomyopathy.[74-77] Limited studies have also examined endoventricular circular restorative procedures as a treatment for nonischemic dilated cardiomyopathy and have shown similar improvements in hemodynamic and ventricular volumes, although the high operative mortality reported in this population has dampened enthusiasm.[78,79] Suggested patient selection criteria include post-infarction patients with New York Heart Association functional class III-IV heart failure, predominant involvement of the anterior, anteroseptal and apical walls with regional asynergy of at least 35% of the ventricle, depressed EF, and end-diastolic and end-systolic volume indices >100 and 60 mL/m^2, respectively. Preoperative functional class and LV volumes appear strongly associated with early and late mortality after SVR.[73,80] Although echocardiography may be used to assess ventricular structure and function, cardiac MRI or CT is preferred by many surgeons to define the region of scar and assess change in LV volumes and EF.

Some concerns have been raised about postoperative increased pulmonary pressures and new or worsening mitral regurgitation, which may be correctible by judicious ventricular sizing and the use of concomitant mitral repair.[81] Other relative contraindications to SVR include multiple areas of infarction, loss of basilar myocardial function, pulmonary hypertension with right ventricular failure, and inoperable coronary disease.[71]

The RESTORE registry group[82] detailed the results of 1198 patients who underwent SVR due to significant post-infarction left ventricular dilation along with concomitant procedures, including coronary artery surgery in 95% and mitral valve repair in 22%, at 12 centers from 1998 to 2003. At baseline, patients had a mean age of 63 years, EF of 30%, and NYHA class of 2.9; the mean time between anterior myocardial infarction and SVR was 4.4 years. The RESTORE investigators reported a 5.3% 30-day mortality following SVR with worse 30-day mortality among those who received a mitral valve procedure (8.7% versus 4.0%) and among patients 75 years or

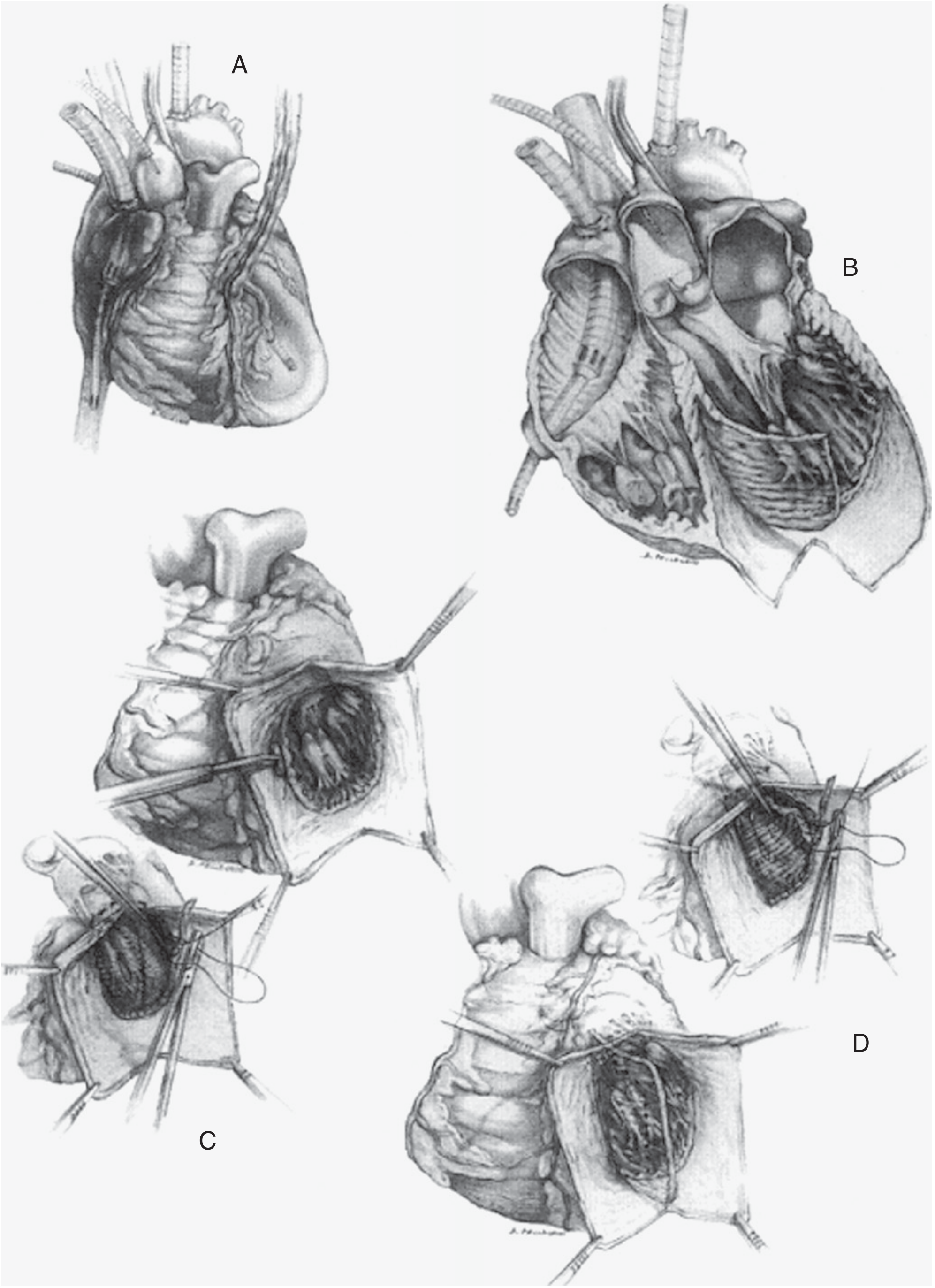

Figure 16–6 Technique of endoventricular circular patch repair. **A,** Lesions exposed under total cardiac arrest after implantation of left internal mammary artery. **B,** Mobilization of the endocardial scar on the septum and up to contractile muscle. **C,** Cryotherapy probe on the limit of resection (in case of ventricular aneurysm). Dacron patch inside the LV on contractile muscle with 2-0 monofilament on pericardial strip. **D,** Autologous endocardial patch is cut in the mobilized septal scar and sutured on contractile muscle. (From Dor V, Sabatier M, DiDonato M, et al: Late hemodynamic results after left ventricular patch repair associated with coronary grafting in patients with post-infarction akinetic or dyskinetic aneurysm of the left ventricle. J Thorac Cardiovasc Surg 1995;110:1291-9, reproduced with permission.)

older (13%). Other risk factors for death included an EF less than 30%, end-systolic volume index greater than 80 mL/m^2, and NYHA class III or IV, which was present at baseline in 40% and 29%, respectively. Functional class and indices of left ventricular size and global systolic function were significantly improved postoperatively. The overall 5-year survival rate was 69%. Unfortunately, the lack of either a coronary surgery alone or medically treated comparator group limits an understanding of the additive benefits of SVR in the LVSD population. However, it appears that HF symptom relief and survival reported with SVR compares favorably with contemporary series among a similar population of patients with dilated ventricles and anterior scar.[83]

The SVR operation is now sufficiently mature and is being performed more and more frequently at an additional cost to treat HF and LVSD. The Society of Thoracic Surgeons (STS)

procedural data base was interrogated to understand the current use and clinical outcomes of patients undergoing SVR.[76] In this 2002 to 2004 national sample of U.S. patients, 731 patients underwent SVR at 141 of the 576 STS hospitals. Importantly, only at 20 of these centers were 10 or more SVR procedures performed. The perioperative complication rates were higher than reported from the RESTORE experience with a 30-day mortality rate of 9.3% and a death or major complication rate of 33.5%. Further analyses are needed to determine the relation between center (and surgeon) volume and surgical outcomes. Based on the above experiences, SVR is increasingly used as a treatment strategy for HF. However, the safety of the procedure across the spectrum of operative skill and disease severity and whether it adds clinical value beyond state-of-the art medical therapy with or without CABG are lacking. The future role of SVR in the management of HF will likely depend on the results of ongoing clinical trials such as STICH.[58]

SURGERY FOR MITRAL REGURGITATION

Mitral regurgitation (MR) is highly prevalent among patients with HF and LVSD and moderate or severe MR has been demonstrated in up to 59% of patients with advanced heart disease.[84,85] The presence and severity of chronic MR are known to be powerful markers of poor prognosis among asymptomatic patients,[86] patients with HF and/or LVSD following acute myocardial infarction,[87] and those with chronic ischemic and nonischemic cardiomyopathy.[88-90] MR is well described as a primary cause of LV dysfunction but is also increasingly recognized as a secondary phenomenon in many patients with cardiomyopathy. Dynamic changes in MR severity in patients with LVSD occur and have been implicated as contributing to acute exacerbations of decompensated HF.[91,92]

Chronic MR can cause, as well as result in, LVSD. Functional MR (defined as abnormal function of normal leaflets in the context of impaired ventricular function) is dependent on a dynamic interplay of structural and functional changes of the left ventricle and mitral valve apparatus, and is influenced by loading conditions.[93] Progressive adverse left ventricular remodeling and dilation augment the predisposing geometric conditions for functional MR. The resulting lateral displacement of the papillary muscles, dilation of the mitral valve annulus, and abnormal leaflet tethering result in leaflet malcoaptation and worsening MR. Furthermore, in patients with ischemic cardiomyopathy, MR may be exacerbated by inferior ischemia causing dysfunction of the posterior papillary muscle. The increased volume load imposed on the left ventricle from MR then leads to more ventricular dilation and sphericity, and a vicious cycle is propagated that contributes to HF progression.[94] Current data show that secondary MR in patients with advanced HF may be associated with changes in the extracellular matrix of the mitral valve leaflets, suggesting that MR may not be purely "functional" and that the valves are not "normal."[95] These considerations have made functional MR an increasing target for intervention in patients with HF.[96] Historical observations in patients with LVSD and MR who underwent mitral valve replacement suggested that correcting MR was associated with high operative risk and worsening HF symptoms and left ventricular function, and tempered any initial enthusiasm for surgical correction.[97] Reports from Bolling and others[98-103] of mitral valve repair (MVR) without replacement led to a resurgence in surgical confidence. MVR is typically performed via a median sternotomy with standard cardiopulmonary bypass with the placement of an undersized flexible annular ring and with preservation of the subvalvular apparatus. Disappointing results owing to persistent MR in some patient subsets led several groups to develop modifications in the surgery—such as the use of an edge-to-edge approach or the addition of chordal or papillary muscle modification.[104-106]

Although national surgical data bases report ever-increasing use and expanding indications of isolated and combined mitral valve procedures,[107,108] available data on MVR as a therapy for HF are mixed. Early hemodynamic, structural, and functional results have been encouraging, but longer-term follow-up studies have questioned whether MVR has any enduring effect on improving quality of life and exercise capacity, and reducing morbidity and mortality rates in HF.[109,110] Particularly among patients with ischemic cardiomyopathy, reports suggest that quality of life and long-term survival are not improved when mitral valve operations are added to coronary revascularization procedures.[111,112] These data, along with an acknowledgment of the growing importance of mitral regurgitation on prognosis, have led to the development of promising percutaneous mitral reparative techniques using either transseptal[113] or coronary sinus[114] approaches. Whether moderate or severe functional MR in patients with HF and LVSD should be managed with medical therapy alone or in combination with revascularization and/or mitral valve surgery remains unclear and awaits prospective, controlled studies although none is currently ongoing.

OTHER NOVEL APPROACHES

Progressive ventricular remodeling, despite the use of neurohormonal antagonists and device therapies, is associated with adverse clinical outcomes in patients with LVSD and HF. This has spurred the development of new surgical approaches to passively restrain the myocardium, with the goals of mechanically minimizing further ventricular dilatation and, in turn, reducing the morbidity and mortality rates.[115] The conceptual approach to mechanically restraining the myocardium derived from experimental work with latissimus dorsi cardiomyoplasty and the Myosplint device (Myocor, Inc.).[116,117] The CorCap Cardiac Support Device (Acorn Cardiovascular, Inc.) has been extensively studied (Fig. 16–7). The CorCap device is made from a mesh-like open-weave polyester fabric and is surgically placed around the heart. In animals, the placement of the CorCap device has been shown to decrease ventricular volumes, enhance contractility, minimize mitral regurgitation, and lead to favorable alteration of cellular and extracellular determinants of ventricular remodeling.[118,119] Initial human studies with the CorCap device in patients with NYHA functional class III-IV HF, low EF, and left ventricular end-diastolic dimension index greater than 30 mm/m^2 suggested that the device could be implanted safely without device-related intraoperative complications and lead to improvements in ventricular size, function, and functional class over a 2-year follow-up period.[120] This early experience led to a randomized clinical trial (the ACORN Pivotal Trial) in 300 patients with NYHA functional class III-IV HF and

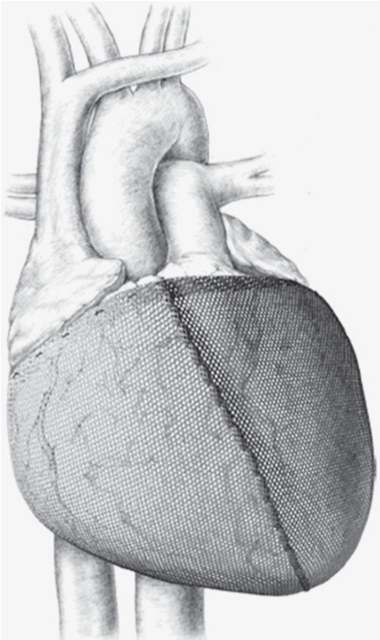

Figure 16–7 CorCap Cardiac Support Device (Acorn Cardiovascular, Inc.) (From Mann DL, Acker MA, Jessup M, et al: Rationale, design, and methods for a pivotal randomized clinical trial for the assessment of a cardiac support device in patients with New York Health Association class III-IV heart failure. J Card Fail 2004;10:185-92, reproduced with permission.)

dilated cardiomyopathy with or without mitral regurgitation requiring MVR.[121] Preliminary data presented at the AHA 2004 Scientific Sessions suggested that patients randomized to CorCap had an improvement in the clinical composite score (driven by the need for further major cardiac procedures) that was associated with decreased left ventricular volumes. However, no significant benefits in rehospitalization rates or mortality were found, which led an FDA advisory panel to recommend against approval of the device pending further studies.

SUMMARY

The surgical management of heart failure associated with left ventricular systolic dysfunction has evolved dramatically since the 1960s. Although reduced ejection fraction and heart failure remain important prognostic determinants of intraoperative and long-term survival, they no longer are considered compelling contraindications to surgery. Significant improvements in medical and device therapy for HF over the last 2 decades have paradoxically led to a growing proportion of patients with LVSD referred for cardiac surgery. Further advances in the surgical management of HF will depend on the development and perfection of new devices and technologies—as well as on a clearer understanding of the role of established surgical options relative to contemporary medical therapy. In this new era, randomized trials of surgical therapies for HF hold great promise for establishing new guidelines and improving patient care.

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Chapter 17

Strategies for Management of Decompensated Heart Failure

Michael M. Givertz, Lynne W. Stevenson, and Wilson S. Colucci

CHAPTER CONTENTS

Heart failure is a common reason for hospital admission, especially in older patients.[1] The majority of patients hospitalized for heart failure have previously been diagnosed with heart failure but have subsequently developed progressive clinical and hemodynamic decompensation that leads to admission. All patients admitted to the hospital with heart failure should undergo a rapid clinical evaluation for risk stratification and for determining the degree of elevation in cardiac filling pressures and the adequacy of systemic perfusion. In addition, effective management should include a careful search for correctable factors. In select cases, hemodynamic monitoring with a pulmonary artery catheter may be indicated for the purpose of initiating and titrating inotropic, vasodilator, and diuretic therapy. Clinical and hemodynamic goals of therapy should be set and specific pharmacologic agents chosen to meet these goals. In cases of refractory heart failure, evaluation for ventricular assist device implantation or cardiac transplantation should be performed in potential candidates. For nontransplant candidates with end-stage heart failure, strategies focusing on symptom management and end-of-life care are appropriate.

TERMINOLOGY

Decompensated heart failure has been defined as heart failure with a relatively rapid onset of signs and symptoms, resulting in hospitalization or unplanned office or emergency room visits.[2] Most of these episodes result from worsening or decompensation of chronic heart failure (Table 17–1).[181,182] Some investigators have arbitrarily divided this group further into patients with *acute* versus *chronic decompensated heart failure*, depending on the time course of worsening symptoms before hospitalization (e.g., days versus weeks or months). However, these terms lack diagnostic accuracy and are limited by the subjectivity of the medical history as provided by the patient or interpreted by the physician. *Stage D heart failure*, as defined by the ACC/AHA guidelines,[3] designates patients with refractory heart failure who might be eligible for specialized, advanced treatment strategies (e.g., mechanical circulatory support, continuous inotropic infusions) or end-of-life care (Fig. 17–1). Approximately 30% of hospitalizations are due to new-onset heart failure, also termed *acute heart failure*, which may be caused by an acute coronary syndrome, uncontrolled hypertension, or acute valvular dysfunction. *Acute pulmonary edema* is a clinical term used to describe patients presenting with rapid worsening of symptoms associated with physical and radiologic findings of pulmonary congestion due to acute elevation of the pulmonary capillary wedge pressure.

EPIDEMIOLOGY

It is estimated that five million persons in the United States are being treated for heart failure, with 550,000 new cases diagnosed each year.[4] The prevalence of heart failure increases dramatically with age, occurring in 1% to 2% of persons aged 45 to 54 and up to 10% of individuals older than age 75.[5,6] Between 1979 and 2002, the number of heart failure hospitalizations per year rose from 377,000 to 970,000, an increase of 157% (Fig. 17–2).[4] Approximately 80% of all heart failure admissions occur in patients older than 65; as a result, heart failure is the leading discharge diagnosis among Medicare beneficiaries with an average length of stay of 5.3 days.[1] Large registries have recently defined the demographics and concomitant diseases associated with acute decompensated heart failure (see Table 17–1). Approximately 50% of patients are women, and nearly 75% have a history of heart failure. Hypertension and coronary artery disease are present in more than 50% of patients, and 30% or more of hospitalized heart failure patients present with diabetes, atrial fibrillation, and renal insufficiency.

Admission to the hospital with heart failure is associated with poor short- and long-term outcomes.[7-9] The Acute Decompensated Heart Failure National Registry (ADHERE)

Table 17–1 Demographics and Co-morbidities of Acute Decompensated Heart Failure

	ADHERE (N = 107,920)	EHFS (N = 11,327)	OPTIMIZE-HF (N = 34,059)
Mean age, years	75	71	73
Women, %	52	47	52
Prior heart failure, %	75	65	87
LVEF < 0.40, %	59	46	52
CAD, %	57	68	50
Hypertension, %	72	53	71
Diabetes, %	44	27	42
Atrial fibrillation, %	31	43	31
Renal insufficiency, %	30	18	NA

ADHERE, Acute Decompensated Heart Failure National Registry[8]; EHFS, Euro Heart Failure Survey[7]; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure registry[181]; LVEF, left ventricular ejection fraction; CAD, coronary artery disease. Adapted from Gheorghiade M, De Luca L, Fonarow GC, et al: Pathophysiologic targets in the early phase of acute heart failure syndromes. Am J Cardiol 2005;96:11G.

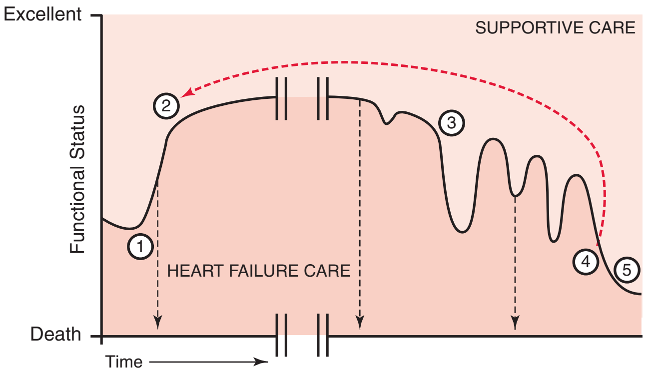


Figure 17–1 Time course of symptomatic heart failure. Patient presents with symptoms of heart failure (1) and treatment is initiated. Stable functional status (2) is maintained for a variable length of time on optimal medical therapy, but subsequently declines (3) with intermittent decompensation that responds to hospital-based therapy or sudden death (*vertical dashed lines*). Patient subsequently develops refractory heart failure (4) requiring consideration of ventricular assist device or cardiac transplant (*dashed line*), or end-of-life care (5). (Adapted from Goodlin SJ, Hauptman PJ, Arnold R, et al: Consensus statement: Palliative and supportive care in advanced heart failure. J Card Fail 2004;10:200.)

tracked outcomes of more than 107,000 heart failure hospitalizations and found an in-hospital mortality rate of 4.0%.[8] In the Euro Heart Failure Survey of more than 11,000 admissions, 6.9% of patients died during a heart failure hospitalization.[7] In community-based studies, crude mortality rates following a heart failure hospitalization range from 8% to 14% at 30 days, and increase to 26% to 37% at 1 year.[9] For survivors, readmission with heart failure is common, ranging from 20% to 25% at 60 days and increasing to nearly 50% at 6 months.[10,11]

Owing to direct medical costs, disability, and loss of employment, heart failure has an enormous economic impact on the U.S. health care system. In 2003, $3.6 billion ($5,456 per discharge) was spent on Medicare beneficiaries for the in-hospital management of heart failure.[12] Estimated treatment costs for all inpatients with heart failure in 2005 were $27.9 billion.

PATHOPHYSIOLOGY

Heart Failure with Reduced versus Preserved Systolic Function

In patients with reduced systolic function (e.g., ejection fraction less than 40%), heart failure reflects an abnormality of contractile function in which the end-systolic pressure volume relation is shifted downward. End-systolic volume, end-diastolic volume, and end-diastolic pressure are increased, and elevated end-diastolic filling pressures are transmitted to the pulmonary venous circulation—resulting in signs and symptoms of pulmonary congestion. In some patients, elevated right-sided filling pressures cause systemic venous congestion, leading to symptoms of abdominal distress. Contractile dysfunction may result from both direct and indirect insults to the myocardium, including loss of myocytes after myocardial infarction, chronic volume or pressure overload, toxins such as alcohol or doxorubicin, or a primary myocardial process (e.g., idiopathic dilated cardiomyopathy). Decreased contractility results in a fall in stroke volume leading to symptoms of decreased cardiac output.

Up to 50% of patients admitted to the hospital with heart failure have normal or near normal left ventricular systolic function (see Table 17–1) and are presumed to have an abnormality in diastolic function.[13,14] The end-diastolic pressure volume relationship may be shifted upward reflecting impaired ventricular filling. Pulmonary vascular and systemic venous congestion results from an increase in left and right ventricular end-diastolic pressures, respectively. Diastolic dysfunction may be due to impaired early relaxation, increased chamber stiffness, or both,[15] and is frequently associated with hypertension and abnormal vascular compliance.[16] Maladaptive volume regulation may also contribute to heart failure with preserved systolic function, and evidence suggests

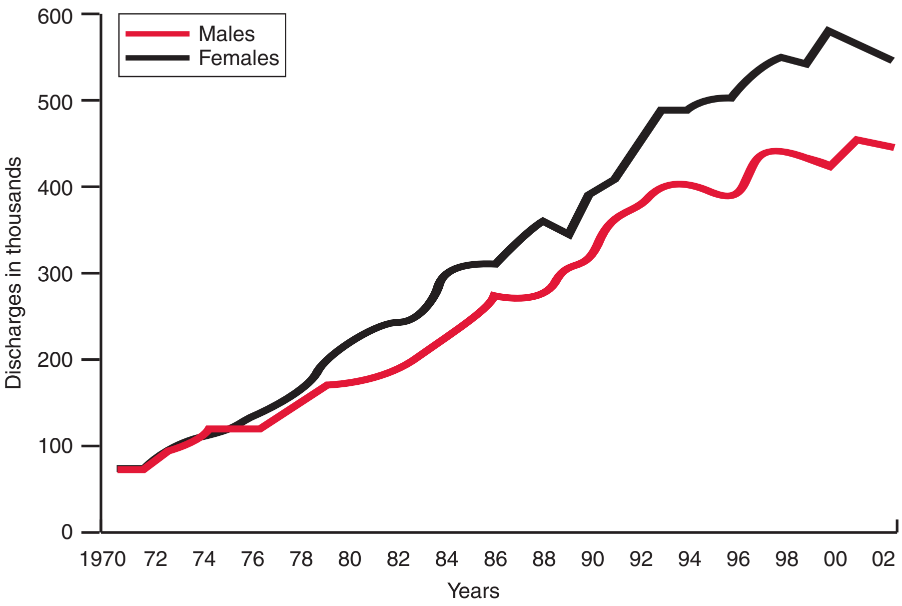


Figure 17–2 Hospital discharges for heart failure by gender in the United States between 1970 and 2002. Among men (*red line*), the number of discharges increased from 90,000 per year in 1970 to 430,000 per year in 2002. Among women (*black line*), the number of discharges increased from 90,000 per year in 1970 to 520,000 per year in 2002. (From Centers for Disease Control and Prevention, National Center for Health Statistics. From American Heart Association. Heart Disease and Stroke Statistics—2005 Update. Dallas, Tex, American Heart Association, 2005.)

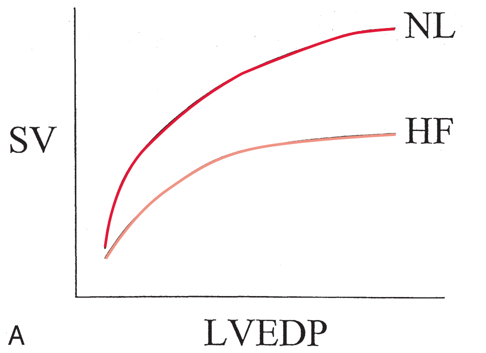
that in elderly hypertensive patients, volume expansion, renal dysfunction, and anemia play important roles in disease progression.[17] Common underlying causes of heart failure with preserved systolic function include ischemia and left ventricular hypertrophy; restrictive, infiltrative, and hypertrophic cardiomyopathies are encountered less frequently.[18,19]

To promote standardization in practice, specific diagnostic criteria for diastolic heart failure have been proposed.[20] However, it is important to remember that systolic heart failure and diastolic heart failure are not mutually exclusive. Although these terms may underscore a predominant pathophysiologic mechanism in the individual patient, many patients with heart failure have abnormalities of both systole and diastole. In patients with ischemic cardiomyopathy, for example, systolic heart failure is caused by both chronic loss of myocardium secondary to infarction and the acute loss of contractility due to ischemia; diastolic heart failure is due to reduced compliance caused by chronic replacement fibrosis and the acute reduction in distensibility by ischemia. For the purposes of patient management, similar principles are often applied to patients regardless of ejection fraction. However, most of the approved diagnostic tools and treatment strategies have been validated in patients with reduced systolic function. In the ADHERE registry, in-hospital mortality was lower in patients with preserved systolic function (2.8% versus 3.9%), although intensive care unit and total length of stay were similar.[21] More complete discussions of diastolic heart failure may be found in Chapter 14 and elsewhere.[22]

Acute Compensatory Mechanisms

In the presence of a primary abnormality in contractile function, the heart depends on a number of compensatory mechanisms to maintain adequate cardiac output and vital organ perfusion (discussed in detail in Chapter 21 of the HD7e). Acutely, ventricular performance may be maintained within normal limits by an increase in preload: the higher the preload, the greater the force of ventricular contraction and the greater the stroke volume. However, the Frank-Starling mechanism is advantageous only if the relationship between preload and contractility is positive. Although this relation may hold true in the setting of acute ischemia with normal chamber dimensions, in chronic systolic heart failure associated with left ventricular dilation, the ventricular function curve may be flat at higher diastolic volumes (Fig. 17–3A). Increased filling may result in little augmentation in cardiac output, and further elevation in end-diastolic pressures may result in increased wall stress, decreased subendocardial perfusion, and worsening mitral regurgitation. Hemodynamic studies in patients with decompensated heart failure have shown that maximal stroke volumes can be achieved by lowering pulmonary capillary wedge pressure (PCWP) into the normal range with parenteral vasodilator (see Fig. 17–3B) and diuretic therapy.[23] This improvement in ventricular function may be due in large part to a reduction in secondary mitral or tricuspid regurgitation, or both, that often complicates dilated ischemic or nonischemic cardiomyopathy, but may also reflect improved myocardial oxygen supply and/or decreased demand.

In addition to the beat-to-beat alterations in contractile function determined by the Frank-Starling mechanism, short-term stabilization of cardiac output or blood pressure may be achieved by activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. Decreased perfusion pressure sensed by carotid sinus and aortic arch receptors results in increased sympathetic and decreased parasympathetic nervous system activity. Consequences of an increase in circulating catecholamines during cardiac decompensation include increased heart rate and contractility to augment cardiac output, systemic vasoconstriction to increase preload and maintain systolic blood pressure, and redistribution of blood flow away from the skin and splanchnic beds to the heart and central nervous system. Activation of the renin-angiotensin-aldosterone system acts in concert with increased sympathetic activity to maintain arterial pressure. Elevated levels of circulating angiotensin II result in systemic vasoconstriction and intravascular volume expansion—the latter effect due to increased aldosterone secretion by the adrenal cortex and



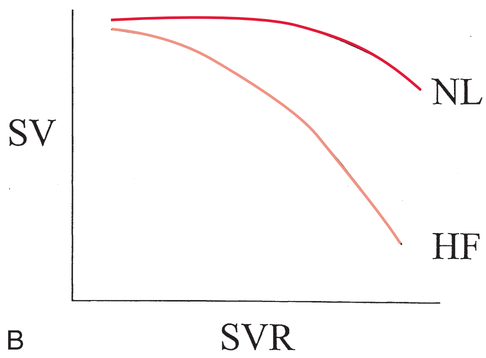


Figure 17–3 Preload and afterload effects on cardiac output/stroke volume in patients with normal (NL) and decreased (HF) left ventricular systolic function. **A,** Ventricular function curve in patients with HF may be flat at higher filling pressures. Thus, further increases in left ventricular end-diastolic pressure (LVEDP) may result in no change in stroke volume (SV). **B,** Alternatively, a reduction in systemic vascular resistance (SVR) by vasodilator therapy may result in a significant increase in SV.

sodium and water retention by the kidney. Elevated circulating levels of arginine vasopressin[24] and endothelin[25] may also contribute to volume expansion and vasoconstriction in decompensated heart failure. In response to an increase in intracardiac pressure and volume, atrial and B-type natriuretic peptides are secreted from cardiac chambers, and act as counter-regulatory hormones by causing vasodilation, diuresis, natriuresis and aldosterone and endothelin antagonism.

Myocardial Injury

Circulating levels of cardiac troponins are increased in the serum of patients with advanced heart failure[26] and may increase further during episodes of acute decompensation in the absence of ischemia.[27] Elevated cardiac troponins predict adverse short-term outcomes, including worsening heart failure and in-hospital mortality, independent of ischemia. These clinical observations raise the possibility that decompensated heart failure is associated with an accelerated loss of cardiac myocytes,[28] which in turn contributes to ventricular remodeling and disease progression. Underlying mechanisms of myocyte loss include necrosis and apoptosis. In addition to ischemia, several apoptotic stimuli are active in the setting of acute decompensation, including oxidative stress, mechanical strain, and neurohormones (e.g., norepinephrine and angiotensin).

Table 17–2 Potentially Reversible Factors Contributing to Decompensation in Patients with Heart Failure

Myocardial ischemia
Uncontrolled hypertension
Tachyarrhythmias or bradyarrhythmias
Noncompliance with medications and/or salt and fluid restriction
Heavy alcohol consumption
Periodic hypoxia (e.g., due to sleep apnea)
Anemia
Recent viral illness
Noncardiac medication causing fluid retention (e.g., NSAID, TZD)
Acute or acute-on-chronic renal failure
Hyperthyroidism

NSAID, nonsteroidal anti-inflammatory drug;
TZD, thiazolidinedione.

COMMON PRECIPITATING FACTORS

Patients with heart failure may be asymptomatic or mildly symptomatic, either because the cardiac impairment is mild or because compensatory mechanisms help to balance or normalize cardiac function. Symptoms of heart failure necessitating hospital admission may develop when one or more precipitating factors increase cardiac workload and disrupt the balance in favor of decompensation (Table 17–2). Specific factors may be identified in 50% to 90% of admissions, and are often correctable.[29,30] In one study of 435 patients admitted nonelectively to an urban hospital with the diagnosis of heart failure, acute chest pain and noncompliance with medications or diet were the precipitating factors in 33% and 21%, respectively.[31] The rate of noncompliance with heart failure medications is particularly high among elderly persons.[32] Failure to take prescribed heart failure medications or adhere to dietary restrictions may result in progressive fluid retention and worsening congestion. However, inadequate therapy is not always caused by patient noncompliance. Physician underuse of angiotensin-converting enzyme (ACE) inhibitors and β-blockers in patients with heart failure is well documented.[21,33] Likewise, digoxin may be withdrawn owing to concerns about toxicity,[34] thereby precipitating heart failure hospitalization.

Cardiac arrhythmias are common in patients with heart failure and often precipitate or exacerbate episodes of moderate-to-severe decompensation.[35,36] Atrial fibrillation with rapid ventricular response results in elevated atrial pressures and may further reduce cardiac output in a patient with limited baseline systolic reserve.[37,38] In patients with ischemic heart disease, tachycardia may induce or intensify ischemia and result in worsening systolic or diastolic function, or both, by increasing myocardial oxygen demands. In addition, a

regular narrow complex tachycardia may occasionally be misinterpreted as sinus in origin when, in fact, atrial flutter or atrioventricular nodal reentry tachycardia is present. In some cases, atrial arrhythmias may be the primary cause of a tachycardia-mediated cardiomyopathy, which is potentially reversible with effective antiarrhythmic therapy or radiofrequency ablation.[39,40] Assessment of thyroid function is warranted in new onset atrial arrhythmias, particularly in the elderly.

Although less common than atrial arrhythmias, sustained or paroxysmal nonsustained ventricular tachycardia often associated with implantable cardioverter-defibrillator (ICD) therapies may precipitate admission to the hospital in a patient with impaired left ventricular function. In patients with heart failure and either reduced or preserved systolic function, symptomatic bradyarrhythmias may be due to intrinsic sinus or atrioventricular nodal dysfunction, adverse drug effects or electrolyte abnormalities (e.g., hyperkalemia). Early recognition and aggressive management of cardiac arrhythmias may be critical to achieving the goal of recompensation. However, it should be remembered that in addition to precipitating heart failure, arrhythmias may be caused by heart failure or result from proarrhythmic effects of drugs used in the management of heart failure. Although not an arrhythmia per se, ventricular dyssynchrony induced by right ventricular pacing is associated with an increased risk of heart failure hospitalization and atrial fibrillation, and warrants consideration of biventricular pacing.[41]

Myocardial ischemia or infarction should be considered as a possible precipitant, not only in patients with known ischemic heart disease presenting with heart failure, but also in patients with other forms of heart disease. For example, patients with previous heart failure secondary to hypertension or valvular heart disease may be well compensated until they develop unstable angina or an acute coronary syndrome. Diabetic patients with silent ischemia or infarction may also present with insidious heart failure. Infection is another common precipitating cause of heart failure. In a study by Tsuyuki and coworkers,[29] 11% of patients with an exacerbation of heart failure had pneumonia. Common viral infections, including influenza A and respiratory syncytial virus (RSV),[42] may also cause acute-on-chronic impairment of ventricular function and precipitate an admission with decompensated heart failure. It is not known whether direct viral infection of the myocardium, myocardial inflammation, or myocardial dysfunction secondary to circulating or local cytokines plays a significant role in such patients. Guidelines recommend that all patients with current or prior symptoms of heart failure receive yearly influenza vaccinations, which have been shown to reduce the rate of influenza by 40% to 50%.[3,43]

Comorbid conditions that are common in patients with heart failure and that may exacerbate symptoms leading to hospitalization include uncontrolled hypertension and anemia (see Table 17–1). In addition, the development of acute or acute-on-chronic renal failure may further impair the ability of patients with heart failure to excrete sodium or free water and thus may exacerbate fluid retention.[44] Other potentially correctable factors contributing to decompensation in heart failure include excessive alcohol consumption,[45,46] and medications that either depress myocardial function (e.g., β-blockers, amiodarone), or cause salt and water retention (e.g., nonsteroidal anti-inflammatory drugs, thiazolidinediones).[47,48] It is essential to search for these and other less common precipitating causes (e.g., hyperthyroidism, pulmonary embolism) in patients admitted to the hospital with heart failure because failure to recognize them may lead to refractory or recurrent heart failure.

GENERAL MANAGEMENT

Initial Patient Evaluation

Regardless of the etiology or underlying precipitant, patients admitted to the hospital for the treatment of heart failure have the potential for hemodynamic deterioration, including the development of cardiogenic shock. Therefore, a rapid bedside evaluation of circulatory status and cardiac rhythm, and assessment for ischemia should be performed even before the medical records or diagnostic studies are reviewed. In addition to ruling out an acute coronary syndrome that may require urgent revascularization or thrombolysis, evidence for marked elevation of intracardiac filling pressures and/or inadequacy of systemic perfusion should be sought. In select cases, inotropic or vasopressor therapy may need to be initiated before obtaining additional diagnostic data or invasive hemodynamic measurements. However, in the majority of patients who are clinically more stable, a complete review of the medical history and a detailed physical examination may provide important information regarding the underlying cause and acute precipitants of heart failure, as well as appropriate targets of therapy.

Risk Stratification

Clinical information obtained at the time of a heart failure admission may help to predict outcomes during the hospitalization and following discharge. Chin and Goldman first sought to determine the risk of a major complication or death in 435 patients admitted nonelectively to an urban university hospital with heart failure.[49] Two thirds of the patients had a previous history of heart failure. Compared with patients with new onset heart failure, these patients were older, and had more comorbidities, lower left ventricular ejection fraction, and lower initial blood pressure. In a multivariate analysis, independent predictors of in-hospital death or major complications that were noted at the time of admission were a systolic blood pressure of less than 90 mm Hg, respiratory rate greater than 30 breaths per minute, serum sodium of less than or equal to 135 mEq/L, and ischemic electrocardiographic changes not known to be old.

Using data from the ADHERE registry, Fonarow and colleagues[8] sought to develop a practical bedside tool for risk stratification of patients with acute decompensated heart failure. Derivation and validation cohorts of more than 65,000 patient records were subjected to classification and regression tree (CART) analysis to identify predictors of in-hospital mortality. Based on this empiric analysis, the single best predictor for mortality was an elevated admission level of blood urea nitrogen (greater than or equal to 43 mg/dL) followed by low systolic blood pressure (less than 115 mm Hg) and high serum creatinine (greater than or equal to 2.75 mg/dL). A simple risk tree identified patient groups with mortality rates

Table 17–3 Risk Stratification for In-Hospital Mortality in the ADHERE Registry

BUN ≥ 43 mg/dL	SBP < 115 mm Hg	Creatinine ≥ 2.75 mg/dL	Mortality, %
–	–	–	2.3
+	–	–	5.7
–	+	–	5.7
+	+	–	13.2
+	+	+	19.8

ADHERE, Acute Decompensated Heart Failure National Registry; BUN, blood urea nitrogen; SBP, systolic blood pressure; –, absent; +, present. Adapted from Fonarow GC, Adams KF, Jr, Abraham WT, et al: Risk stratification for in-hospital mortality in acutely decompensated heart failure: Classification and regression tree analysis. JAMA 2005;293:572.

ranging from 2.3% to 19.8% (Table 17–3). Additional clinical and laboratory predictors of adverse outcomes obtained at the time of hospital admission include presence of congestion,[50] ischemic etiology,[51] reduced ejection fraction,[21] anemia,[52] hyponatremia, elevated B-type natriuretic peptide (BNP) levels,[53,54] and positive cardiac troponins.[27]

Clinical Assessment of Intracardiac Filling Pressures

Most hospitalizations for decompensated heart failure occur because of congestion rather than low cardiac output.[7,55] Although congestion is often readily apparent in patients with acute heart failure, marked elevation in filling pressures may be underappreciated in patients with chronic heart failure.[56] In one study of nonedematous heart failure patients, unrecognized hypervolemia was present in 65% and predicted reduced survival.[57] Increased capacity for pulmonary lymphatic drainage resulting from chronic pulmonary congestion may lead to clinical situations in which PCWPs exceeding 30 to 35 mm Hg are tolerated. Conversely, a history of dyspnea on exertion is common in patients with heart failure and lacks the specificity to detect elevated cardiac filling pressures. Alternative mechanisms of dyspnea include decreased pulmonary function, increased ventilatory drive, and respiratory muscle fatigue.[58,59] Not surprisingly, investigators have been unable to demonstrate a close correlation between symptoms of exercise tolerance and measures of resting left ventricular performance in patients with heart failure. However, dyspnea on minimal exertion or at rest, including orthopnea and paroxysmal nocturnal dyspnea, are more specific historical clues to increased left-sided filling pressures in patients with known left ventricular failure. In patients with biventricular heart failure, abdominal discomfort, early satiety, nausea, vomiting, and anorexia suggest increased right-sided filling pressures. In addition, changes in baseline symptoms in an individual patient may suggest a clinically important worsening of heart failure.

Rales are a relatively specific, but insensitive, sign of pulmonary vascular congestion. In a series of patients with chronic heart failure and reduced ejection fraction, rales were present in only 60% of patients with an elevated PCWP.[60] However, rales were also detected in 16% of patients with normal PCWP and may be due to coexistent pulmonary or pleural disease. In the ADHERE registry, rales were present in two thirds of patients with acute decompensated heart failure.[21] Signs of increased right-sided filling pressures, including jugular venous distention, ascites, and peripheral edema, are relatively reliable indicators of increased left-sided filling pressures.[56] However, in specific clinical situations such as right ventricular infarction or pulmonary embolism, jugular venous distention may occur without signs of left-sided congestion. Significant interobserver variability regarding the extent of jugular venous elevation limits its usefulness at the bedside.[61] Both ascites and peripheral edema are less sensitive signs of volume overload than jugular venous distention, particularly in young adults, and may be preceded by the development of tender hepatomegaly. A third heart sound may suggest the presence of previously undiagnosed cardiomyopathy, but its presence is neither sensitive nor specific for acute decompensated heart failure. Increased intensity of the pulmonic component of the second heart sound in association with a holosystolic murmur suggests pulmonary hypertension due to chronic heart failure and associated mitral and/or tricuspid regurgitation.

Rarely, experienced examiners may use the bedside Valsalva maneuver with sphygmomanometric determination of arterial blood pressure response to help clarify the left ventricular filling pressure.[62] However, limited patient effort due to dyspnea or discomfort, and arrhythmias may interfere with this examination. An automated device that quantifies the blood pressure response to the Valsalva maneuver,[63] as well as contrast-enhanced and tissue Doppler echocardiographic techniques[64] have been developed for the noninvasive determination of left ventricular filling pressures. In addition, intrathoracic impedance monitoring[65] and plasma volume analysis[57] are new methods to assess fluid status in heart failure patients. However, prospective data demonstrating the usefulness of these new "tools" in patient management are lacking.

Like the physical examination, routine chest radiography has been shown to be an insensitive clinical tool for demonstrating congestion in the setting of chronic heart failure.[66] In one study, 68% of patients with advanced heart failure and PCWP ≥ 25 mm Hg had minimal or no evidence of pulmonary congestion on admission chest radiographs.[67] When present, however, interstitial or alveolar edema suggests markedly elevated filling pressures. Bilateral or unilateral pleural effusions are common in acute decompensated heart failure,[68] and may not necessarily respond to diuresis. In these instances, ultrasound-guided thoracentesis[69] or chest tube thoracostomy may be necessary to relieve respiratory distress and improve arterial oxygenation.

Clinical Assessment of Systemic Perfusion

Fatigue and weakness, which are common complaints in patients with heart failure, may be due to reduced cardiac output and poor perfusion of skeletal muscles. In addition, abnormal endothelium-dependent vasodilation, respiratory muscle fatigue, and altered skeletal muscle structure and function may contribute to exercise intolerance in heart failure.[70] However, fatigue is a nonspecific symptom that may be caused by many noncardiopulmonary diseases (e.g., anemia, renal failure, depression), disordered sleep (e.g., sleep apnea, restless legs), drugs (e.g., β-blockers, sedatives) or electrolyte abnormalities. If a patient is admitted to the hospital with decompensated heart failure, mental obtundation or anuria are highly suggestive of critically reduced perfusion. A more subtle history of altered mentation such as lack of concentration or memory may be obtained from a family member. In severe low-output states, the patient may appear anxious or diaphoretic or exhibit signs of air hunger. Patients with advanced heart failure may be cachectic from a low-output state and catabolic/anabolic imbalance,[71] whereas those with more recent onset heart failure will be well nourished. Other physical signs of acute hypoperfusion include cool extremities, digital or circumoral cyanosis, and marked hypotension with a rapid, thready pulse. Pulsus alternans signifies advanced myocardial disease and tends to be present during tachycardia.

In measuring the blood pressure noninvasively, it is important to deflate the cuff slowly, listening closely to define the systolic blood pressure and pulse pressure, especially in patients with atrial fibrillation. Prior studies have shown that when the pulse pressure is less than 25% of the systolic blood pressure, there is a high likelihood that the cardiac index is below 2.2 liters/minute/m^2.[56] Thus, in a patient with severe heart failure, a blood pressure of 100/90 mm Hg may be more worrisome than a blood pressure of 80/50 mm Hg. However, preliminary data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) demonstrate lack of correlation between the estimated and invasive assessment of cardiac index.[72]

Laboratory Assessment

Routine chemistry and hematology studies obtained on admission may be helpful in the initial assessment of patients with decompensated heart failure, and in formulating a therapeutic plan. Dilutional hyponatremia may result from a combination of sodium restriction, aggressive diuresis, and an impaired ability to excrete free water.[73,74] Increased circulating levels of renin and vasopressin are also important mediators of hyponatremia in heart failure.[24] Although ACE inhibitors alone or in combination with loop diuretics may acutely correct hyponatremia in severely ill patients with heart failure, overactivity of the renin-angiotensin-aldosterone system may predispose these same patients to the development of hypotension, worsening renal function, and hyperkalemia on initiation of, or rechallenge with, an ACE inhibitor. Use of nonsteroidal anti-inflammatory agents should be avoided in hyponatremic patients because they may aggravate hemodynamic abnormalities and cause worsening renal function.[47]

Prolonged, high-dose diuretics may predispose patients to hypokalemia and hypomagnesemia,[75] both of which are associated with an increased risk of ventricular arrhythmias. Hyperkalemia may result from marked reductions in glomerular filtration rate and inadequate delivery of sodium to the distal renal tubule. Excess total body potassium may be exacerbated by the use of ACE inhibitors, potassium supplements, or aldosterone receptor antagonists.[76] The risk of hyperkalemic arrhythmias appears to be highest during potassium replacement, when intracellular potassium concentrations are still low; and hyperkalemia is a common cause of iatrogenic morbidity, and even mortality, during a heart failure hospitalization. Other laboratory abnormalities that may complicate management of decompensated heart failure include elevated liver enzymes, hyperbilirubinemia, and a prolongation of the prothrombin time. If right-sided heart failure is long-standing, cardiac cirrhosis may result in hypoalbuminemia and an exacerbation of extravascular fluid accumulation as well as inappropriate vasodilation. Low serum prealbumin levels and elevated C reactive protein levels are pro-inflammatory markers associated with cachexia in patients with end-stage heart failure.

In patients with chronic heart failure, blood urea nitrogen and serum creatinine levels are elevated secondary to reductions in renal blood flow and glomerular filtration rate. Decreased renal perfusion can precipitate bouts of acute tubular necrosis and lead to reduced renal mass. Other factors contributing to the presentation of combined cardiac and renal dysfunction, or "cardiorenal syndrome,"[77] include an altered balance of vasoconstrictor and vasodilating hormones, and comorbidities such as diabetes and hypertension. In patients with advanced heart failure, several commonly used classes of drugs including inhibitors of the renin-angiotensin-aldosterone system and diuretics may exacerbate renal impairment. During a heart failure hospitalization, approximately 25% of patients will develop worsening renal function defined variably as an increase in serum creatinine by greater than or equal to 0.3 mg/dL or 25% above baseline. The mechanisms underlying worsening renal function remain unknown, but are believed to include diuretic-induced reductions in glomerular filtration rate and neurohormonal activation. From a clinical standpoint, worsening renal function often results in interruption of diuretic therapy and discontinuation of other disease-modifying agents such as ACE inhibitors (Table 17–4). Worsening renal function is an independent predictor of increased length of stay and excess mortality both in-hospital and post-discharge.[44]

B-Type Natriuretic Peptides

B-type natriuretic peptide (BNP) is synthesized and secreted by the cardiac ventricles in response to an increase in wall stress or filling pressure. N-terminal pro-BNP (NT-proBNP) is an inactive fragment that results from cleavage of BNP from its pro-hormone. Both BNP and NT-proBNP can be used to help diagnose and risk stratify patients with acute decompensated heart failure.[53,54,78] In patients with chronic heart failure and reduced systolic function, BNP levels are elevated in relation to disease severity and provide strong independent prognostic information. Plasma BNP levels are also elevated in patients with heart failure and preserved systolic function, correlate with wall stress[79] and may predict survival.[80] In

Table 17–4 Potential Consequences of Worsening Renal Function During a Heart Failure Admission

Hospital discharge is delayed
Diuretic doses are decreased, often despite persistent congestion
ACE inhibitors, ARBs, and aldosterone receptor antagonists are discontinued
Noncardiac medications (e.g., antibiotics) are dose-adjusted
Positive inotropic agents are initiated to "increase renal perfusion"
Pulmonary artery catheter is placed to assess hemodynamics
Foley catheter is placed to record urine output
Renal ultrasound is ordered to rule out post-obstructive uropathy

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

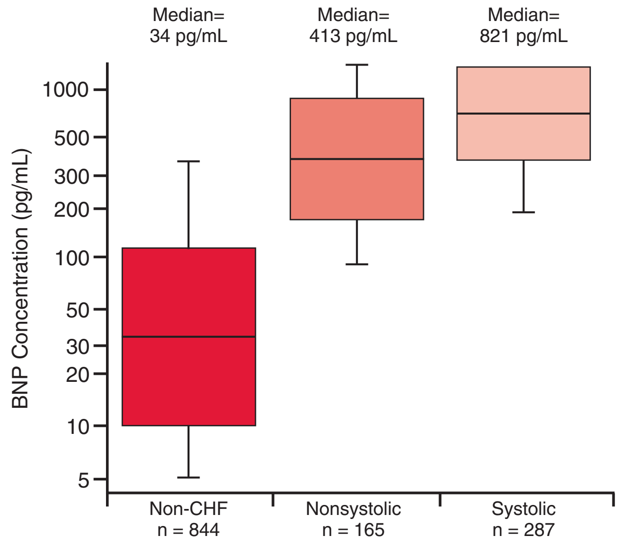


Figure 17–4 Box and whisker plots showing median BNP levels in patients presenting to the emergency department with dyspnea not due to heart failure (non-CHF) compared with patients with a final adjudicated diagnosis of diastolic (nonsystolic) versus systolic heart failure. (From Maisel AS, McCord J, Nowak RM, et al: Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003;41:2010.)

the acute setting, low or normal BNP levels (e.g., less than 100 pg/mL) have a reasonably high negative predictive value for excluding heart failure as the cause of dyspnea.

In one study of patients presenting to the emergency room with shortness of breath, patients with diastolic heart failure had lower BNP levels compared with those with systolic heart failure (median 413 pg/mL and 812 pg/mL, respectively) (Fig. 17–4).[81] However, BNP added only modest discriminatory value in differentiating these two groups. In patients with advanced heart failure, BNP levels correlate only modestly with LV filling pressures,[82] and the diagnostic accuracy of BNP for predicting an elevated PCWP is limited by a high false-negative rate. BNP levels decrease in parallel with a reduction in filling pressures during acute diuretic and vasoactive therapy, and change in BNP (Fig. 17–5A) and predischarge BNP (see Fig. 17–5B) are independent predictors of subsequent events.[53] In practice, however, BNP levels can vary substantially between individuals with the same degree of heart failure (Table 17–5). For example, natriuretic peptide levels are higher in women, increase with age and renal insufficiency, and decrease with obesity.[83] Currently, there is no proven role for BNP-guided therapy in the inpatient setting, although a BNP level obtained at the time of presentation to the emergency room may decrease resource use.[84]

Noninvasive versus Invasive Management

Although practice patterns differ greatly, the majority of patients with acute decompensated heart failure can be managed safely and effectively on a cardiac telemetry unit without invasive monitoring. Admission to an intensive care unit should be reserved for patients with: (1) hemodynamic instability requiring titration of vasoactive therapy, placement of a pulmonary artery catheter or mechanical circulatory support; (2) unstable cardiac rhythms requiring cardioversion, defibrillation, or temporary pacing; (3) acute respiratory failure requiring noninvasive or mechanical ventilation; or (4) severe renal failure requiring electrolyte management and urgent consideration of dialysis. For all patients, clinical goals of therapy should be set (Table 17–6), including the relief of symptoms related to congestion such as orthopnea and abdominal fullness, and improvement in symptoms of low cardiac output (e.g., fatigue, anorexia). Physical findings of volume overload, including jugular venous distention, lower extremity edema, hepatomegaly, and ascites, should also be targets of therapy. Despite optimal care, not all patients will be free of congestion at the time of discharge, including patients in whom diuresis is limited by worsening renal function, hypotension, or both. If possible, the patient should be discharged with a systolic blood pressure above 80 mm Hg and warm extremities.

The insertion of a pulmonary artery catheter for the purpose of hemodynamic monitoring may be helpful in select patients, but is not recommended for the routine management of acute decompensated heart failure. As described above, a reasonable noninvasive assessment of volume status and adequacy of perfusion may be obtained by history and physical examination. If severely elevated filling pressures, critically reduced perfusion, or both, is evident, placement of a pulmonary artery catheter should not take precedence over initiation of appropriate therapy (e.g., parenteral diuretics, positive inotropic or vasopressor agents). In select cases, hemodynamic measurements will be helpful in the choice and titration of parenteral agents to optimize loading conditions and improve clinical status rapidly. However, routine clinical use of the pulmonary artery catheter for heart failure management has not proved effective in observational or controlled clinical studies.

In an observational study of critically ill patients with a variety of conditions including acute respiratory failure, multisystem organ failure, and heart failure, right heart catheterization was associated with an increased 30-day mor-

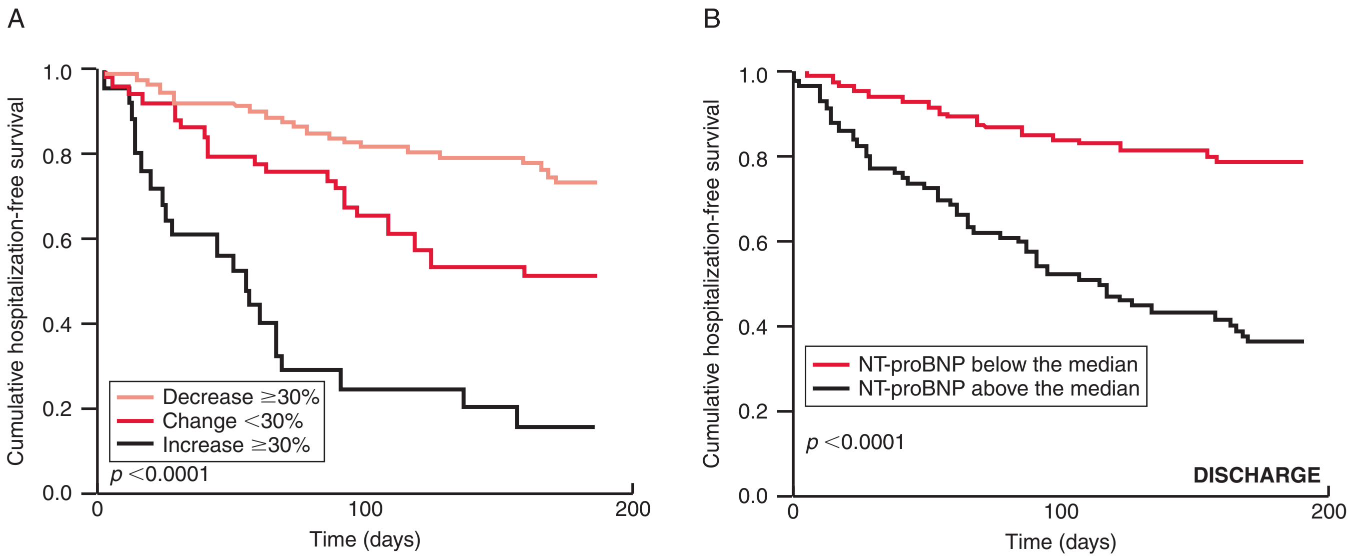


Figure 17–5 Hospitalization-free survival according to **A,** patterns of response of N-terminal proBNP (NT-proBNP) during in-hospital treatment of heart failure: decreased by ≥30% of baseline (*pink line*), changed by less than 30% (*red line*) or increased by ≥30% (*black line*); **B,** NT-proBNP level at discharge (median 4137 pg/mL). (From Bettencourt P, Azevedo A, Pimenta J, et al: N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168.)

Table 17–5 Biological and Clinical Variability of B-Type Natriuretic Peptide Levels

Increased Levels	Decreased Levels
Older age	Overweight and obesity
Female gender	Diastolic heart failure
Acute or chronic kidney disease	Pharmacologic therapy
Non-heart failure conditions	Angiotensin receptor blockers
Myocardial infarction	β-Blockers
Pulmonary embolism	Spironolactone
Cor pulmonale	Device therapy
	Cardiac resynchronization therapy
	Ventricular assist device

Table 17–6 General Goals in the Treatment of Acute Decompensated Heart Failure

Goal	Clinical Endpoint	Hemodynamic Endpoint
Decrease left-sided filling pressure	Absence of orthopnea, dyspnea on minimal exertion	PCWP ≤ 16 mm Hg
Decrease right-sided filling pressure	Absence of gastrointestinal symptoms	RAP ≤ 8 mm Hg
	Resolution of edema or hepatomegaly	
	JVP < 8 cm H_2O	
Increase cardiac output	Proportional pulse pressure >25%	CI ≥ 2.2 L/min/m^2
Decrease peripheral resistance	Warm extremities	SVR 1000 to 1200 dynes-sec·cm^{-5}
Maintain adequate perfusion pressure	SBP ≥ 80 mm Hg	SBP ≥ 80 mm Hg
	Stable renal function	

CI, cardiac index; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SBP, systolic blood pressure; SVR, systemic vascular resistance.

tality rate and increased use of resources.[85] However, this study was methodologically flawed (e.g., use of post-hoc matching, lack of control for the collection, interpretation and use of hemodynamic data), and in the subgroup of patients with heart failure, the relative hazard of death was 1.02 ($P = 0.94$).

The ESCAPE Trial sought to determine whether pulmonary artery catheter use is safe and improves clinical outcomes in patients hospitalized with severe heart failure.[86] Four hundred and thirty three patients were randomized to receive therapy guided by clinical assessment and pulmonary artery catheter or clinical assessment alone. The target of therapy in

Table 17–7 Impact of Pulmonary Artery Catheter versus Clinical Assessment During Heart Failure Hospitalization: The ESCAPE Study

Variable	PAC Group	CLIN Group	P value
Days alive out of hospital, mean	133	135	0.99
Mortality at 180 days, %	20.0	17.4	0.95
Hospitalizations per patient, median	2.0	2.0	NA
Δ Global symptom score	25 ± 25	24 ± 24	0.45
Weight loss, kg	–4.0 ± 5.4	–3.4 ± 4.2	0.32
Δ Creatinine, mg/dL	0.0 ± 0.4	0.1 ± 0.1	0.02
Line infection, %	1.9	0	0.03

ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness;[86] PAC, pulmonary artery catheter; CLIN, clinical assessment. Adapted from Nohria A, Mielniczuk LM, Stevenson LW: Evaluation and monitoring of patients with acute heart failure syndromes. Am J Cardiol 2005;96:32G.

both groups was resolution of congestion, with additional hemodynamic targets (right atrial pressure 8 mm Hg, PCWP 15 mm Hg) set for the invasive group. Therapy in both groups led to substantial reduction in signs and symptoms of congestion, but there was no difference in morbidity or mortality rates in the two groups (Table 17–7). In a meta-analysis of randomized clinical trials in critically ill patients that included data from ESCAPE, use of the pulmonary artery catheter had no effect on hospital length of stay or mortality.[87]

Despite these negative findings, there may be select indications for invasive hemodynamic monitoring during treatment of acute decompensated heart failure. These include evidence of severe hypoperfusion, marked congestion at rest associated with acute ischemia, infarction or renal failure, fluid retention that is refractory to high-dose or combination diuretics, hypoxemia with coexistent cardiac and pulmonary disease, and shock of unclear etiology. In addition, hemodynamic assessment is routine in considering patients for cardiac transplantation, in whom the degree and reversibility of pulmonary hypertension[88] are important predictors of post-transplant outcomes.[89] Similarly, invasive hemodynamic measurements are helpful in the evaluation of patients for ventricular assist device implantation, either as a bridge to cardiac transplant or permanent therapy, and in their perioperative management (see Chapter 18). The benefits of pulmonary artery catheter use may be more evident at centers experienced with hemodynamic monitoring for advanced heart failure.[64]

Hemodynamic Profiles

Initial *clinical assessment* of cardiac filling pressures and systemic perfusion can be used to categorize patients into broad *hemodynamic profiles* that help guide medical management and provide prognostic information.[50] If the patient is found to be *clinically well compensated* despite presenting with shortness of breath at rest, an evaluation for intermittent ischemia or paroxysmal arrhythmias is indicated. In addition, noncardiac causes of dyspnea, both pulmonary and extrapulmonary, as well as psychological causes, such as anxiety, should be considered.

The most common hemodynamic profile encountered in patients with acute decompensated heart failure is pulmonary and/or systemic venous *congestion with normal perfusion*. In these patients, symptoms will generally respond to diuresis using an intravenous loop diuretic or the combination of a loop and thiazide diuretic. If the patient does not respond to initial attempts at diuresis, vasodilator therapy, (either oral or intravenous), may require titration because elevated filling pressures can be exacerbated by systemic and pulmonary vasoconstriction in addition to volume expansion. If the patient is already taking an ACE inhibitor or angiotensin receptor blocker, the dose should be titrated after an effective diuresis has been achieved, while monitoring closely for orthostatic hypotension, worsening renal function, or both. In select patients, a combination of vasodilators may be used such as isosorbide dinitrate, hydralazine, or an angiotensin receptor blocker in addition to an ACE inhibitor. Large pleural effusions or ascites that do not respond to diuresis may require thoracentesis or paracentesis, respectively. Symptomatic goals of diuretic therapy include resolution of orthopnea and dyspnea at rest or on minimal exertion. For patients in whom a pulmonary artery catheter has been placed, hemodynamic goals are discussed subsequently.

Hypoperfusion without pulmonary venous congestion, manifested by progressive fatigue and anorexia and often accompanied by azotemia, may precipitate hospitalization in patients with severe heart failure. Use of positive inotropic agents is often necessary when perfusion is critically reduced, although open-label and controlled studies as well as registry data[90] suggest that short-term exposure to an inotrope is associated with an increased risk of adverse events, including death. Use of parenteral vasodilators may be considered if systemic vasoconstriction is suspected, but are usually poorly tolerated if filling pressures are not also elevated. Vasodilators can precipitate hypotension[11] and lead to worsening renal function[91] in the setting of low or normal cardiac filling pressures. In addition, further reflex neurohormonal activation can lead to clinically significant arrhythmias. In patients with underlying ischemic heart disease, decreased coronary artery perfusion pressure and reflex tachycardia may aggravate ischemia. Some patients may develop significant hypoperfusion secondary to overdiuresis. In this situation, the judicious use of intravenous fluids may be considered, but patients should be observed closely to avoid onset of congestive symptoms.

For patients who present with the combination of *pulmonary and/or systemic venous congestion and inadequate*

systemic perfusion, simultaneous reduction in filling pressures and optimization of systemic vascular resistance (see Fig. 17–3B) can generally be accomplished with intravenous vasodilator therapy, with intermittent or continuous infusion diuretics, over 1 to 3 days. Once clinical goals are achieved, conversion to an oral regimen that maintains stability of clinical and laboratory parameters may require an additional 24 to 48 hours of treatment.

Hemodynamic Goals of Therapy

For patients in whom a pulmonary artery catheter has been placed to guide treatment, the ideal goal of parenteral therapy in the management of decompensated heart failure is to achieve an effective cardiac output at relatively normal filling pressures. For patients with severe hemodynamic compromise, a reduction in filling pressures and systemic vascular resistance (SVR) is often associated with a 30% to 50% increase in forward stroke volume. Although the optimal hemodynamics for a given patient cannot be predicted with certainty, specific goals of hemodynamically guided therapy should be set (see Table 17–6). A PCWP of less than or equal to 16 mm Hg is appropriate for most patients with chronic heart failure, whereas a slightly higher filling pressure may be necessary to maintain cardiac output in the setting of acute myocardial infarction (i.e., decreased left ventricular compliance without significant dilation). A right atrial pressure less than or equal to 8 mm Hg is optimal in most settings as long as the PCWP is not reduced excessively. With exceptions such as right ventricular infarction and pulmonary embolism associated with hypotension, a higher right atrial pressure may be required. Maintaining a cardiac index greater than or equal to 2.2 L/minute/m^2 is often necessary to avoid cerebral, renal, or hepatic hypoperfusion. However, lower cardiac indices may cause relatively little organ dysfunction if the low-output state has developed gradually. SVR is optimal in the range of 1000 to 1200 dynes-sec·cm^{-5}. Although cardiac output may be increased further with additional lowering of the SVR (i.e., in the range of 800 to 900 dynes-sec·cm^{-5}), a reflex increase in sympathetic tone may result in unwanted tachycardia, orthostatic hypotension, and renal dysfunction.[91] Finally, the above goals should be aimed for while maintaining a systolic blood pressure ≥80 mm Hg or a mean arterial pressure ≥60 mm Hg.

It should be remembered that thermodilution measurements may overestimate the cardiac output in patients with low-output states, possibly due to a loss of the cold indicator across the myocardium. Thermodilution measurements may also be unreliable in the setting of significant tricuspid regurgitation or marked respiratory variation, although one study showed a good correlation between thermodilution and Fick outputs in patients with chronic heart failure and moderate-to-severe tricuspid regurgitation.[92] Alternatively, mixed venous oxygen saturations may be used to calculate cardiac output using the Fick equation with oxygen consumption measured by a metabolic rate meter. Given that oxygen consumption may be influenced markedly by infection, other stresses, or sedation, and has been shown to vary greatly among adults at the time of cardiac catheterization, the use of "assumed" Fick outputs is not recommended. An alternative is to follow changes in the mixed venous oxygen saturation to estimate cardiac output trends.[93]

In choosing an initial parenteral agent, particular attention should be paid to the systemic vascular resistance (see following discussion of specific agents). Patients with an elevated SVR will generally tolerate initiation of a vasodilator such as nesiritide or nitroglycerin without hypotension and will achieve significant hemodynamic benefit. On the other hand, patients with a low SVR (e.g., secondary to concomitant sepsis or anesthesia) often will not tolerate further vasodilation without developing symptomatic hypotension. Dobutamine, which provides inotropic support in addition to mild vasodilation, is the preferred initial agent in this situation. An alternative choice would be dopamine at lower doses (3 to 5 mcg/kg/minute). Higher doses may increase filling pressures and elevate the SVR by stimulating α-adrenergic receptors. In patients with an SVR in the normal range, both vasodilators and positive inotropes are often effective and may be used in combination. An alternative to the combination of a vasodilator and inotrope is the phosphodiesterase inhibitor, milrinone, which exerts both direct inotropic and vasodilator effects in patients with decompensated heart failure. The incidence of hypotension is higher with milrinone, owing to greater peripheral vasodilation.

FLUID MANAGEMENT

Parenteral Diuretic Therapy

The initiation of an effective diuresis is integral to the management of elevated cardiac filling pressures associated with acute decompensated heart failure. For patients admitted to the hospital, this can best be accomplished with parenteral diuretics because the intravenous route will more reliably deliver high drug concentrations to the renal tubular lumen.[94,95] Furosemide is the most widely used loop diuretic, although bumetanide and torsemide are also available for patients with documented intolerance or unresponsiveness to furosemide. Furosemide can be given intravenously in doses ranging from 20 to 240 mg (or higher) depending on the patient's diuretic history, and as frequently as every 4 to 6 hours. Addition of a thiazide-type diuretic such as metolazone (2.5 to 10 mg orally) or chlorothiazide (250 to 500 mg intravenously) often potentiates the diuresis. A continuous infusion of furosemide (e.g., 5 to 40 mg per hour) may be used to treat refractory fluid retention.[96] A Cochrane review of 8 trials in 254 patients found that urine output was significantly greater with a continuous infusion, although the difference was modest (mean difference 271 mL per 24 hours). Less tinnitus and hearing loss occurred with continuous infusion.[97] The addition of hypertonic saline to intravenous furosemide may result in more rapid achievement of dry weight, but this novel strategy remains to be tested in a multicenter study.[98]

For patients with hypokalemia requiring significant potassium supplementation, a potassium-sparing diuretic such as spironolactone or triamterene may be used. Aldosterone receptor antagonists are additionally beneficial in the management of fluid retention associated with cirrhosis,[99] and chronic therapy with spironolactone reduces morbidity and mortality in patients with severe heart failure.[100] For patients with marked fluid overload unresponsive to diuretics or for those who develop worsening renal function requiring

discontinuation of diuretics, ultrafiltration or hemodialysis (if there is coexistent renal failure) may be considered (see later).

In the setting of acute pulmonary edema, the rapid clearance of congestion by parenteral diuretics is mediated by natriuresis and diuresis, decreased intravascular volume, and systemic vasodilation. In patients with acute or chronic decompensated heart failure, the goals of diuretic therapy include the elimination of edema and orthopnea (see Table 17–6). Reduction in atrial and ventricular diastolic pressures reduces wall stress and ventricular volumes and may improve subendocardial perfusion and reduce valvular regurgitation, respectively. Frequent reevaluation of clinical status and renal function, as well as hemodynamics if available, is necessary to guide frequency and duration of therapy. Mild azotemia may be tolerated to achieve hemodynamic compensation, but may identify high-risk patients that require closer follow-up after discharge. Fluid and sodium restriction and cautious replacement of potassium and magnesium are important adjunctive measures that should not be overlooked. Once treatment goals are achieved, the patient should be converted to an oral diuretic regimen that maintains stable weight and renal function. Adverse effects of aggressive diuresis include electrolyte abnormalities and associated arrhythmias, worsening renal function,[44] metabolic alkalosis, muscle cramps, and ototoxicity.[101]

Ultrafiltration

Ultrafiltration removes excess plasma volume without causing a significant change in electrolytes. In patients with chronic heart failure and diuretic resistance, ultrafiltration improves symptoms, neurohormones, and hemodynamics without hypotension.[102] Reductions in peripheral and pulmonary edema, and a subsequent increase in diuretic efficacy have been reported. Recent pilot studies in acute decompensated heart failure suggest that early ultrafiltration is associated with greater fluid removal and symptom relief than medical therapy alone,[103] and may decrease length of stay and readmission rates.[104] The effects of ultrafiltration on renal function and outcomes were tested in a large, multicenter randomized trial (UNLOAD). Preliminary data from UNLOAD suggest that ultrafiltration removes more fluid and reduces readmission rates compared with standard diuretic therapy in patients with acute decompensated heart failure.[104a] Additional data on safety and cost effectiveness are needed.

VASOACTIVE THERAPY

Nitroglycerin

When administered intravenously, nitroglycerin has an immediate onset of action and a plasma half-life of 1 to 4 minutes. It is cleared by the vascular endothelium, hydrolyzed in the blood, and metabolized in the liver. At lower infusion rates, its main cardiovascular effect is venodilation with a resultant fall in ventricular volumes and filling pressures (Table 17–8). At higher infusion rates, nitroglycerin also causes arterial dilation resulting in decreases in both pulmonary and systemic vascular resistance.[11,105] Nitroglycerin may be of particular use in patients who are refractory to diuretic therapy and continue to manifest elevated filling pressures, have disproportionate right-sided failure or unstable ischemia, or are intolerant to nitroprusside.

Table 17–8 Hemodynamic Effects of Parenteral Vasodilators

	PCWP	SVR	CO
Nitroglycerin	↓↓	↔↓	↑↔↓
Nesiritide	↓↓	↓	↑
Nitroprusside	↓↓	↓↓	↑↑
Milrinone	↓↓	↓↓	↑↑

CO, cardiac output; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

Intravenous nitroglycerin is usually started at a low infusion rate of 20 to 30 mcg/minute, and increased by 10 to 20 mcg/minute every 5 to 10 minutes until the desired response is observed or a dose of 400 mcg/minute is reached. If a pulmonary artery catheter is present, cardiac filling pressures and SVR are used to guide titration, although careful noninvasive monitoring of blood pressure may be adequate in the absence of severely reduced perfusion. As with other vasodilators, use of nitroglycerin may be limited by hypotension requiring cessation of the drug, intravenous fluids, or leg elevation. In addition, vasodilation may be associated with headache, flushing, and diaphoresis. Patients with significant right-sided heart failure may be resistant to the acute administration of nitroglycerin, but will often respond following diuresis. Pharmacologic tolerance to nitroglycerin may also develop,[106,107] and preventive strategies include avoidance of excessive dosing, limiting fluid retention, and the use of intermittent dosing.

Nesiritide

As discussed above, BNP levels are elevated in patients with heart failure, correlate with severity of illness, and provide prognostic information. The physiologic effects of BNP include vasodilation, diuresis, natriuresis, and antagonism of the renin-angiotensin-aldosterone and endothelin systems.[80] Based on these favorable actions, recombinant human BNP (nesiritide) was developed for the treatment of heart failure. In early clinical studies in patients with mild-to-moderate heart failure, nesiritide was shown to exert potent vasodilator (see Table 17–8)[108] and modest natriuretic effects,[109] and to improve dyspnea and fatigue when compared with placebo.[110] To compare the efficacy and safety of nesiritide with another vasodilator, the Vasodilation in the Management of Acute CHF study randomized 489 patients with acute decompensated heart failure to receive intravenous nitroglycerin or nesiritide in addition to standard therapy.[11] At 24 hours, the reduction in PCWP was greater with nesiritide than nitroglycerin (-8.2 versus -6.3 mm Hg, $P = 0.04$) with no evidence of tachyphylaxis, whereas there was a similar improvement in dyspnea in both groups. The duration of symptomatic hypotension, which occurred in approximately 5% of patients in both groups, was greater with nesiritide; headache and abdominal pain were more common with nitroglycerin. In 2001, the U.S. Food and Drug Administration approved nesiritide for the treatment of patients with acute decompensated heart failure and dyspnea at rest or with minimal activity. Although it may be initiated in the emergency depart-

ment, nesiritide is more commonly used in patients who remain symptomatic despite intravenous diuretic therapy.

The recommended starting dose of nesiritide is a 2 mcg/kg intravenous bolus followed by a continuous infusion of 0.01 mcg/kg/minute. Although the dose may be increased by 0.005 mcg/kg/minute to a maximum of 0.03 mcg/kg/minute to achieve the desired clinical or hemodynamic effects (see Table 17–6), higher doses are associated with increased rates of hypotension[11] and worsening renal function.[91] Thus, nesiritide is not recommended for use in patients with a systolic blood pressure <90 mm Hg or in those suspected of having low cardiac filling pressures. If there is uncertainty regarding volume status, an initial infusion rate of 0.005 mcg/kg/minute without a bolus is recommended. If symptomatic hypotension occurs, the infusion rate should be immediately decreased or discontinued. In patients with the cardiorenal syndrome, there is no evidence that nesiritide improves renal function or enhances diuresis.[111]

In patients awaiting cardiac transplant with secondary pulmonary hypertension, continuous nesiritide infusion for days to weeks has been used alone or in combination with a positive inotrope (e.g., dobutamine) to lower pulmonary artery pressures and pulmonary vascular resistance.[112] It is recommended that nesiritide be discontinued several hours before induction of cardiac anesthesia to avoid the development of catecholamine-refractory vasoplegia following cardiopulmonary bypass.[113] There is no proven role for intermittent outpatient infusions of nesiritide in patients with chronic decompensated heart failure.

Nitroprusside

For patients with decompensated heart failure characterized by low cardiac output, high filling pressures and elevated SVR, nitroprusside can be used either alone or in combination with a positive inotropic agent to rapidly improve hemodynamics.[114] The drug's potent vasodilator effect is mediated by the local production of nitric oxide.[115] The onset of action is rapid (i.e., 1 to 2 minutes), making it an ideal agent for use in urgent situations that require rapid dose titration and a predictable hemodynamic effect. Nitroprusside is a balanced arterial and venous dilator, and reduces both filling pressures and systemic and pulmonary vascular resistance (see Table 17–8). Stroke volume and cardiac output increase, and pulmonary artery, pulmonary capillary wedge and right atrial pressures decrease (Fig. 17–6). In patients with chronic heart failure, heart rate is generally unchanged or may fall due to reflex sympathetic withdrawal.[105] Nitroprusside infusion may be started at a rate of 10 to 20 mcg/minute and increased by 20 mcg/minute every 5 to 15 minutes until the hemodynamic goals are achieved while maintaining a systolic blood pressure ≥80 mm Hg. Doses of 300 mcg/minute or higher are seldom required and increase the risk of toxicity. Cardiac output and SVR should be measured frequently during titration.

Nitroprusside is a potent vasodilator and its use may be limited by hypotension. In patients with ischemic heart disease, decreases in coronary perfusion pressure accompanied by reflex tachycardia may worsen myocardial ischemia. In patients with acute decompensated heart failure, hemodynamic deterioration may occur immediately following the withdrawal of nitroprusside due to a transient increase in systemic vascular tone (Fig. 17–7).[116] Hemodynamic rebound may be avoided by initiating oral vasodilator therapy before nitroprusside withdrawal. Other adverse effects of nitroprusside are due to the accumulation of its metabolites, cyanide and thiocyanate.[117] Cyanide toxicity, which is most likely to occur in patients with hepatic dysfunction or following prolonged infusions, results in lactic acidosis and methemoglobinemia, and may manifest as nausea, restlessness, and dysphoria. If cyanide toxicity is suspected, the infusion should be stopped and serum levels checked. Thiocyanate toxicity may occur gradually in patients with renal insufficiency, and is manifested by nausea, confusion, weakness, tremor or seizures, and rarely, coma. If mild, cessation of the infusion is usually sufficient; in severe cases, hemodialysis may be necessary.

Dobutamine

Dobutamine is a direct-acting synthetic sympathomimetic amine that stimulates β_1-, β_2-, and α-adrenergic receptors in the myocardium and vasculature.[118] Its primary cardiovascular effect is to increase cardiac output by increasing myocardial contractility (Table 17–9). Although dobutamine does not stimulate dopaminergic receptors in the kidney, renal blood flow often increases in proportion to the increase in cardiac output. In contrast to other β-adrenergic agonists (i.e., isoproterenol), the positive inotropic effect of dobutamine is associated with less increase in heart rate. The drug causes modest decreases in left ventricular filling pressure and systemic vascular resistance (see Fig. 17–6) due to a combination of direct vascular effects and the withdrawal of sympathetic tone. Dobutamine also directly improves left ventricular relaxation via stimulation of myocardial β-adrenergic receptors.[119]

Dobutamine may be a useful agent for the initial management of patients with acute or chronic decompensated heart failure characterized by a low cardiac output and end-organ dysfunction. It can be initiated at a dose of 2 mcg/kg/minute and titrated upward by 1 to 2 mcg/kg/minute until clinical or hemodynamic goals are achieved or a dose-limiting event, such as unacceptable tachycardia or an arrhythmia, occurs. Doses of 3 to 5 mcg/kg/minute are often adequate for good clinical response. Maximum effects are usually achieved at a dose of 15 mcg/kg/minute, although higher infusion rates may occasionally be used. The inotropic response to dobutamine may be attenuated owing to desensitization of the β-adrenergic receptor pathway.[120] If the maximally tolerated infusion rate of dobutamine does not result in a sufficient increase in cardiac index or improved end-organ perfusion, a second positive inotropic agent such as milrinone may be added.[121] In patients with elevated cardiac filling pressures and/or SVR, the coadministration of a vasodilator may be required. In patients who remain hypotensive on dobutamine, high-dose dopamine may be added while considering mechanical support and cardiac transplantation (see Chapter 18), if indicated.

Dobutamine may increase heart rate, thereby limiting the dose that can be infused. However, in some patients with very depressed cardiac output, the improvement in hemodynamic function may cause a withdrawal of sympathetic tone such that heart rate actually decreases. Hypotension is uncommon, but can occur in patients who are hypovolemic. Arrhythmias, including supraventricular and ventricular tachycardia, may limit the dose. Likewise, myocardial ischemia secondary to increased myocardial oxygen consumption may occur. Some patients with severe heart failure may show pharmacologic tolerance to dobutamine, or tolerance may develop after several days of a continuous infusion. In patients awaiting

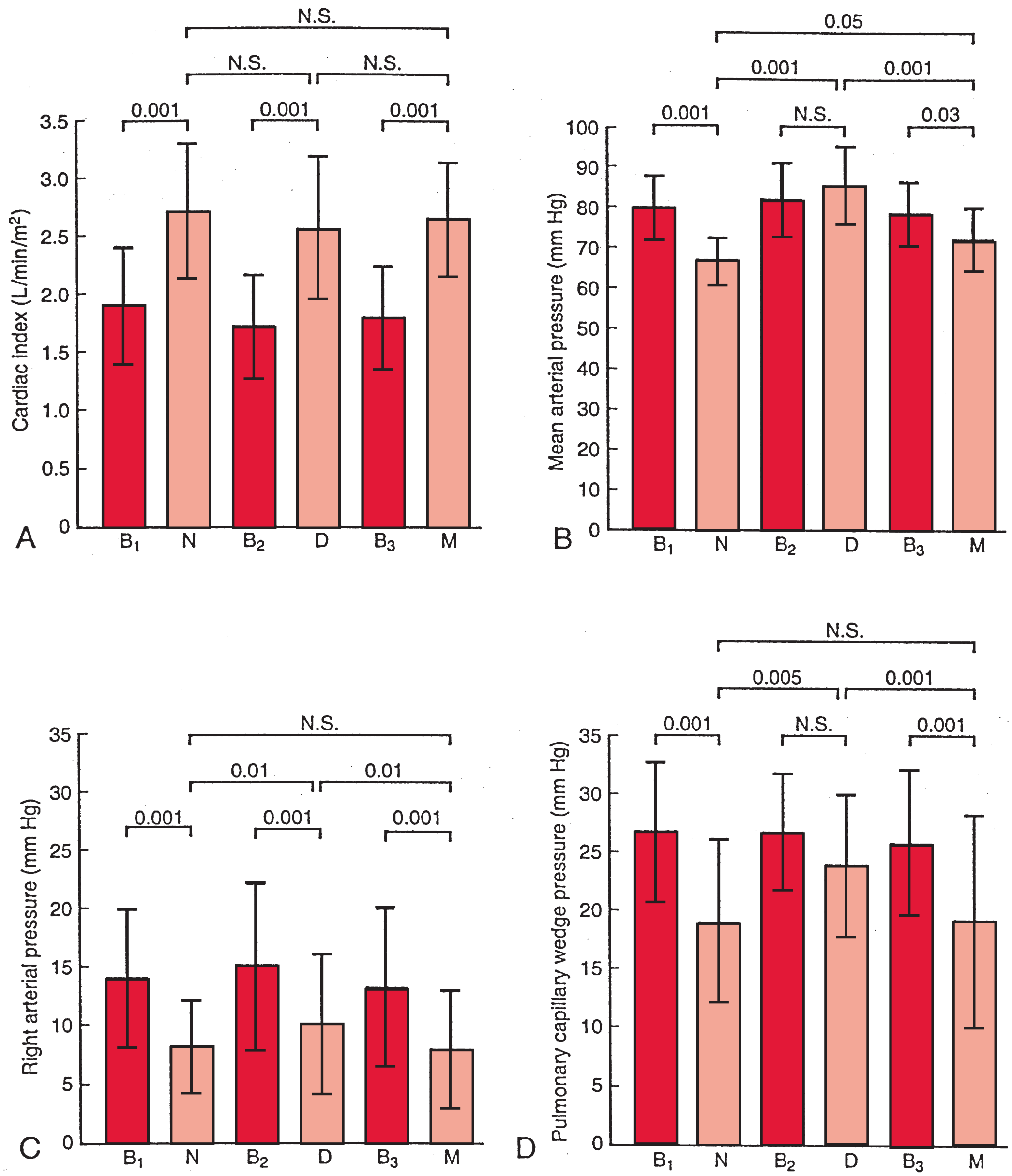


Figure 17–6 Comparative effects of nitroprusside (N), dobutamine (D), and milrinone (M) on cardiac index, mean arterial pressure, right atrial pressure, and pulmonary capillary wedge pressure in patients with severe heart failure (B_1, B_2, and B_3 = baseline measurements). The three agents were administered in doses that caused comparable increases in cardiac index (**A**). Under these conditions, nitroprusside and milrinone significantly reduced arterial pressure, but dobutamine had no effect (**B**). All three agents reduced right atrial pressure (**C**), although the effect of dobutamine was slightly less pronounced. Both nitroprusside and milrinone significantly reduced pulmonary capillary wedge pressure (**D**), and this effect was more pronounced than the effect of dobutamine. (Adapted Monrad ES, Baim DS, Smith HS, et al: Milrinone, dobutamine, and nitroprusside: Comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. Circulation 1986;73:III168-III174.)

cardiac transplantation, chronic dobutamine therapy may cause hypersensitivity myocarditis[122] leading to hemodynamic deterioration. In these situations, the addition or substitution of a phosphodiesterase inhibitor may be necessary.

Milrinone

In myocardium and vascular smooth muscle, inhibition of the membrane-bound enzyme, phosphodiesterase (PDE), results in an increase in intracellular cyclic AMP. Milrinone is a selective inhibitor of the type III isoform of PDE. In the myocardium, milrinone exerts both positive inotropic and lusitropic effects.[123] Milrinone is also a potent vasodilator in the systemic and pulmonary circulation (see Fig. 17–6).[124] In patients with acute decompensated heart failure, milrinone increases cardiac output due to an increase in stroke volume (see Table 17–9). Balanced arterial and venous dilation causes decreases in right atrial, pulmonary artery, pulmonary capillary wedge, and mean arterial pressures (see Table 17–8). For a comparable increase in cardiac output, milrinone decreases

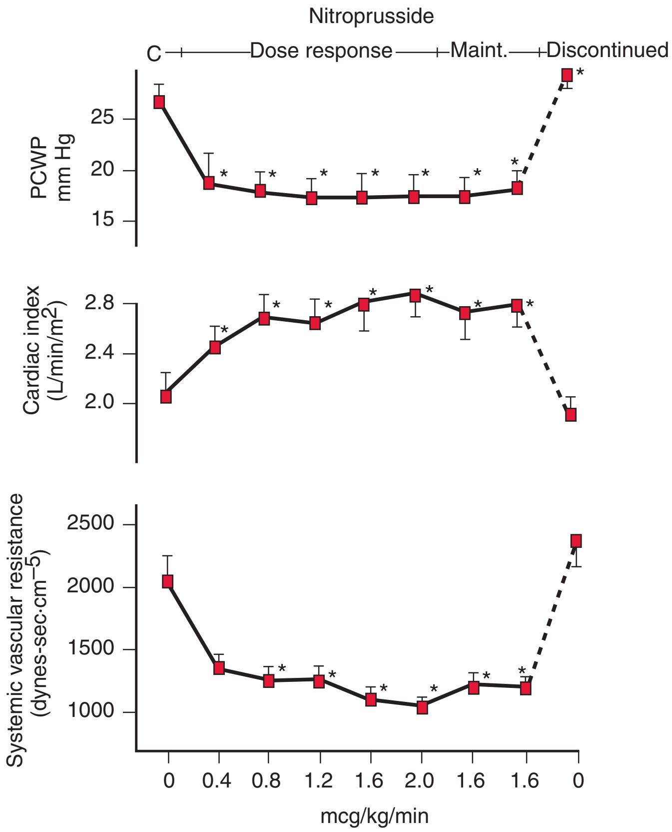


Figure 17–7 Hemodynamic rebound following discontinuation of nitroprusside in patients with moderate-to-severe heart failure. Graphs show changes in PCWP (*top panel*), cardiac index (*middle panel*) and systemic vascular resistance (*bottom panel*) during dose response, maintenance (Maint.) and discontinuation (Discontinued) of nitroprusside infusion. Thirty minutes following discontinuation, PCWP and systemic vascular resistance increased significantly above, and cardiac index decreased significantly below control values. (Adapted from Leier CV, Bambach D, Thompson MJ, et al: Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin, and nitroprusside in patients with congestive heart failure. Am J Cardiol 1981;48:1115.)

SVR and left ventricular filling pressure to a greater extent than dobutamine. Conversely, for a comparable decrease in arterial blood pressure, milrinone increases cardiac output to a greater extent than nitroprusside.[125]

Milrinone may be useful for the treatment of refractory heart failure characterized by low cardiac output, high filling pressures and elevated or normal SVR. It may also be used as a bridge to cardiac transplant[126] or end of life,[127] especially in patients who develop tolerance to dobutamine, or to test pulmonary vasoreactivity in patients with secondary pulmonary hypertension being evaluated for cardiac transplant.[124] The positive inotropic effects of milrinone are additive to those of digoxin and may be synergistic with those of dobutamine.[128]

In patients with heart failure, milrinone is usually administered as a 25 to 50 mcg/kg intravenous bolus over 10 minutes followed by a constant infusion at 0.25 to 0.75 mcg/kg/minute, although an infusion may be initiated without a bolus. Although the pharmacologic half-life of milrinone is less than 1 hour in patients with heart failure, it is prolonged in the setting of renal dysfunction, and physiologic effects of discontinuation may not be fully apparent for over 12 hours. Thus, for patients undergoing cardiac surgery, it is recommended that milrinone be discontinued several hours before induction of anesthesia to avoid the development of vasoplegia. The major dose-limiting effects of milrinone are tachycardia and atrial or ventricular arrhythmias.[10] In addition, relatively volume-depleted patients may not tolerate the vasodilator effects of this agent and will experience hypotension requiring drug discontinuation. Other adverse effects of milrinone include liver function test abnormalities, fever, and nausea.

Table 17–9 Hemodynamic Effects of Positive Inotropic Agents

	+dP/dt	PCWP	SVR	CO
Dobutamine	↑↑	↓	↓	↑
Dopamine (low dose)	↔	↔	↓	↔↑
Dopamine (high dose)	↑↑	↑	↑↑	↑↔↓
Milrinone	↑	↓↓	↓↓	↑

CO, cardiac output; +dP/dt, maximum rate of rise of left ventricular systolic pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

The occurrence of adverse events with short-term therapy has led clinicians to question the wisdom of using inotropes routinely in the management of decompensated heart failure. In a large study of patients admitted with an exacerbation of systolic heart failure, a 48-hour infusion of milrinone did not reduce the subsequent need for hospitalization and was associated with an increased risk of arrhythmias and sustained hypotension compared with placebo.[10] However, this study was criticized for enrolling patients who did not require inotropic therapy.

Dopamine

Dopamine is the immediate biosynthetic precursor of epinephrine and norepinephrine, and has both cardiac and vascular sites of action depending, in part, on the dose used.[129] At low doses (i.e., 1 to 3 mcg/kg/minute), dopamine directly activates dopaminergic receptors in the kidney, causing vasodilation. A small increase in cardiac output and decrease in SVR may also be observed (see Table 17–9). The resultant increase in renal blood flow leads to increased urine output and sodium excretion. At moderate doses (i.e., 3 to 8 mcg/kg/minute), dopamine is a weak partial agonist at myocardial β_1-receptors and exerts positive chronotropic and inotropic effects. In addition, increased release of norepinephrine from nerve terminals in the vasculature may result in stimulation of α-adrenergic receptors and a mild vasoconstrictor effect. At moderate-to-high doses (i.e., 5 to 20 mcg/kg/minute), peripheral α-adrenergic stimulation becomes apparent, resulting in vasoconstriction and increases in mean arterial pressure and systemic vascular resistance. As dopaminergic vasodilator effects in the kidney are overshadowed, renal blood flow decreases and urine output may decline.

In patients with acute decompensated heart failure, dopamine is occasionally used at low infusion rates to

improve renal function by increasing renal blood flow. Increased water and sodium excretion results in a decrease in cardiac filling pressures. To achieve clinical or hemodynamic goals, low-dose dopamine may be combined with other inotropic or vasodilator therapy.[121] In patients with significant hypotension or frank cardiogenic shock, higher doses of dopamine are used to increase SVR. When it is necessary to use vasoconstrictor doses of dopamine in the setting of myocardial failure, it is often useful to add dobutamine to augment the level of positive inotropic support beyond that provided by dopamine alone. If used alone at vasoconstrictor doses in patients with advanced heart failure, dopamine may increase both left and right heart filling pressures.[130] To counteract increased afterload and peripheral venoconstriction, high-dose dopamine may be combined with a vasodilator such as nitroglycerin.

As with dobutamine, the inotropic response to dopamine may be attenuated in patients with advanced heart failure[131] due to β-receptor downregulation and depletion of myocardial catecholamine stores.[132] Although generally well tolerated at low doses, higher infusion rates of dopamine may result in sinus tachycardia and supraventricular or ventricular arrhythmias. Other adverse effects of dopamine include digital gangrene in patients with peripheral arterial disease, tissue necrosis at sites of infiltration, and nausea at high doses.

Epinephrine and Norepinephrine

Epinephrine stimulates β_1- and β_2-adrenergic receptors in the myocardium, thereby causing marked positive chronotropic and inotropic responses. It also has potent agonist effects at vascular β-adrenergic receptors, causing increased arterial and venous constriction. Because of this latter effect, epinephrine (like high-dose dopamine) plays a minor role in the management of acute decompensated heart failure, except when complicated by severe hypotension. Epinephrine may be useful for the treatment of low cardiac output, with or without bradycardia, immediately following cardiopulmonary bypass or cardiac transplantation.[133] Continuous infusions may be started at a low dose, 0.5 to 1 mcg/minute, and titrated upward to 10 mcg/minute, as needed. The use of epinephrine may be limited by tachycardia, arrhythmias, ischemia due to increased myocardial oxygen consumption, and oliguria from renal vasoconstriction. In the setting of cardiac arrest, epinephrine may be used as per the Advanced Cardiovascular Life Support guidelines (1 mg intravenous push every 3 to 5 minutes) to manage ventricular fibrillation or pulseless ventricular tachycardia unresponsive to initial countershocks, asystole, or pulseless electrical activity.[134] Epinephrine infusion (2 to 10 mcg/minute) can also be used to treat patients with profound bradycardia while awaiting placement of an external or temporary transvenous pacemaker. An alternative agent to epinephrine for the treatment of shock-refractory ventricular fibrillation is vasopressin, which may be given once as a 40-unit intravenous push.[134]

The myocardial and peripheral vascular effects of norepinephrine are similar to those of epinephrine except that norepinephrine causes little stimulation of vascular β_2-adrenergic receptors and, therefore, causes more intense vasoconstriction. Norepinephrine may be used to provide temporary circulatory support in the setting of severe hypotension (e.g., following cardiac surgery or with cardiogenic shock complicating acute myocardial infarction).[135] Norepinephrine is infused at doses of 2 to 10 mcg/minute. As with epinephrine, the use of norepinephrine may be limited by arrhythmias, myocardial ischemia, and renal impairment.

Digoxin

Although digoxin can be given intravenously, it is seldom used as a positive inotropic agent in the management of acute or chronic decompensated heart failure. However, digoxin may occasionally be used to control heart rate in a patient with heart failure complicated by atrial fibrillation or atrial flutter with rapid ventricular response. In this setting, digoxin is given as a 0.5 to 1 mg intravenous load in divided doses over 12 to 24 hours. If the patient is markedly symptomatic with hemodynamic compromise, synchronized electrical cardioversion should be attempted. Less commonly, intravenous amiodarone or ibutilide may be tried for urgent chemical cardioversion[136] while the patient is supported with an inotrope, vasodilator, or both. Because there is a significant risk of proarrhythmia (torsades de pointes) with ibutilide administration, patients should be monitored closely on telemetry.

ADJUSTMENT OF ORAL MEDICATIONS

Renin-Angiotensin System Inhibitors

For patients without symptomatic hypotension or evidence of hypoperfusion, ACE inhibitors can often be initiated or increased empirically. However, in patients with hyponatremia or a resting systolic blood pressure of less than 90 mm Hg, marked hypotension may develop with the initial dose of an ACE inhibitor. In such patients, therapy should be initiated with low-dose captopril (e.g., 6.25 mg). For patients who have been stabilized on an intravenous vasodilator such as nesiritide or nitroprusside, ACE inhibitors should be titrated upward gradually as the intravenous vasodilator is weaned. With captopril, the dose can be increased every 6 to 8 hours until the desired level of vasodilation is achieved, while avoiding orthostatic vital signs. In patients for whom medication compliance has been suboptimal, switching over to a once-daily ACE inhibitor (e.g., lisinopril) at the time of discharge may be helpful. Not all patients, however, tolerate ACE inhibition. Approximately 25% of patients with advanced heart failure who were previously treated with an ACE inhibitor develop a circulatory or renal limitation (e.g., symptomatic hypotension, worsening renal function, or hyperkalemia) to continued use. ACE inhibitor intolerance identifies patients with severe heart failure and poor prognosis.[137]

An angiotensin receptor blocker (ARB) may be substituted for an ACE inhibitor in patients who develop a persistent and troublesome cough not due to heart failure or concomitant pulmonary disease (see Chapter 14). Updated ACC/AHA guidelines also suggest that although ACE inhibitors remain the first choice for inhibition of the renin-angiotensin system in heart failure, ARBs are a reasonable alternative.[3] Furthermore, addition of an ARB may be considered in persistently symptomatic patients with reduced ejection fraction already treated with an ACE inhibitor.[138]

Nitrates and Hydralazine

The addition of isosorbide dinitrate to captopril frequently reduces SVR and ventricular filling pressures more effectively than does captopril alone. In some patients who cannot tolerate captopril, isosorbide dinitrate may be used alone as an effective vasodilator.[139] Isosorbide dinitrate is typically initiated at a dose of 10 mg three times daily and may be increased up to a total daily dose of 180 to 240 mg. The development of nitrate tolerance may be minimized by use of a nitrate-free interval of 10 to 12 hours.[140] As with ACE inhibitors, compliance may be enhanced by switching to a once-daily formulation (e.g., isosorbide mononitrate) before discharge.

For patients in whom weaning from intravenous agents has been difficult, or in whom ACE inhibitors are not tolerated or do not adequately optimize clinical or hemodynamic status, hydralazine may be of value, often in combination with oral nitrates. The African-American Heart Failure Trial (A-HeFT) showed that adjunctive therapy with hydralazine and isosorbide dinitrate improves survival in blacks with advanced heart failure.[141] The usual starting dose of hydralazine is 10 to 25 mg, and the maximal dose is 75 to 100 mg three or four times daily. Side effects are common, and in A-HeFT included headache (48%), dizziness (29%), and nausea (10%); hydralazine-induced lupus is rare. Hydralazine may also precipitate ischemic events in patients with heart failure caused by ischemic cardiomyopathy (see Chapter 5).[142]

β-Blockers

As discussed in Chapter 14, all patients with heart failure and reduced ejection fraction should be treated with a β-blocker unless there is a contraindication (e.g., moderate-to-severe reactive airways disease) or documented intolerance to treatment. Although there are no studies demonstrating the long-term benefits of β-blockade in patients with heart failure and preserved systolic function, most patients with diastolic heart failure have another indication for anti-adrenergic therapy such as ischemic heart disease or hypertension. In the management of acute decompensated heart failure, a frequent question that arises at the time of hospital admission is what to do with background β-blocker therapy. At present, only empirical recommendations can be made based on the severity of presentation. If the patient is on a stable dose of β-blocker and presents with mild decompensated heart failure, the outpatient dose of β-blocker should be continued. If the acute decompensation is moderate in severity and/or precipitated by recent β-blocker titration, the dose should decreased by at least 50%. If the patient presents with severe heart failure with hemodynamic instability that is not due to tachyarrhythmias or uncontrolled hypertension, β-blocker should be withheld until clinical and hemodynamic stabilization has been achieved.

If treatment with a β-adrenergic agonist such as dobutamine is being considered, it is important to remember that chronic β-blocker therapy, especially with carvedilol, may attenuate the hemodynamic response[143] and, thus, should be discontinued. For patients with atrial or ventricular arrhythmias complicating severe decompensated heart failure, the hemodynamic effects of milrinone do not appear to be compromised by concomitant β-blocker therapy.[143] For stable patients with new onset heart failure who have not yet received a β-blocker, cautious initiation before discharge appears safe, does not increase length of stay, and improves the use of chronic β-blockade.[144]

Oral Diuretics

Once fluid balance has been restored, the selection of an oral diuretic dose is empiric, and further adjustment is usually required both in the hospital and after discharge. It should be noted that patients have a different salt and fluid intake at home than in the hospital. As a first approximation, the dose of intravenous diuretic that was effective may be given as an oral dose twice daily. Daily weights should be recorded along with fluid intake and output. Renal function and electrolytes should be monitored closely until discharge. Pre-discharge education regarding home weight monitoring and flexible diuretic dosing reduces the likelihood of a heart failure readmission.[145]

OTHER MANAGEMENT ISSUES

Sodium and Fluid Restriction

The majority of patients with advanced heart failure should receive a sodium-restricted diet (2 g/day) while in the hospital, except in rare cases in which oral nutrition is of overriding importance. In addition, education regarding sodium content of food may be enhanced during an admission.[146] Patients with intense neurohormonal activation, as indicated by a low serum sodium, may have marked thirst. Diuresis may intensify thirst initially, but this usually improves over 1 to 2 weeks as a lower volume status is maintained and the thirst mechanism "resets" itself. Restricting fluid intake to 2 liters per day is usually adequate for most hospitalized patients. In cases of severe or symptomatic hyponatremia, fluid should be restricted to 1 liter per day, and administration of oral salt or normal saline and diuretics may be necessary.

Oxygen Supplementation

In the absence of acute respiratory failure, concomitant pulmonary or pulmonary vascular disease, or significant right-to-left shunting, patients with chronic heart failure rarely exhibit arterial desaturation. In such patients, supplemental oxygen does not improve systemic oxygen delivery and has the drawbacks of causing airway irritation and limiting movement. The use of nasal oxygen is often empiric and may provide subjective benefit, perhaps through suppression of central dyspnea. In some patients, oxygen may decrease elevated pulmonary vascular resistance and improve right heart function, although 100% oxygen has been shown to depress cardiac output and increase PCWP in patients with moderate-to-severe heart failure.[147] Supplemental oxygen is recommended in patients with acute myocardial infarction complicated by heart failure, and alone or in combination with continuous positive airway pressure in patients with central or obstructive sleep apnea, respectively.[148,149]

Ventricular Arrhythmias

Premature ventricular contractions and nonsustained ventricular tachycardia may occur in up to 80% of patients

hospitalized with heart failure. Their appearance correlates with the severity of heart failure and all-cause mortality, but there is no evidence that suppression with antiarrhythmic agents improves prognosis. Ventricular arrhythmias that compromise perfusion or cause symptoms should be treated. Suppression with agents such as lidocaine is rarely necessary and is often complicated by toxicity. Amiodarone is the antiarrhythmic of choice in patients with decompensated heart failure, and can be given as an intravenous or oral load,[150] while monitoring closely for toxicity related to acute negative inotropic effects. Less efficacious alternatives include oral mexiletine or dofetilide. Patients with chronic ischemic or nonischemic cardiomyopathy with reasonable likelihood of 1-year survival should be considered for placement of an ICD based on primary prevention studies[151,152] and revised Centers for Medicare and Medicaid Services guidelines (see Chapter 15 and Appendix 2).

Anticoagulation

Although patients with a low ejection fraction and a dilated ventricle are at increased risk of thromboembolism, there are no prospective data to support the routine use of anticoagulation in chronic heart failure.[153] Anticoagulation is indicated for patients with additional risk factors such as atrial fibrillation, a history of an embolic event, or echocardiographic evidence of intracavitary thrombus. Consideration should also be given to anticoagulating patients with spontaneous echocontrast, apical akinesis or aneurysm, or acute heart failure due to peripartum cardiomyopathy or fulminant myocarditis. During hospitalization, such patients can be treated with intravenous unfractionated heparin, which can be discontinued for invasive procedures. Screening for venous thromboembolism is indicated when patients present with unilateral or asymmetric bilateral lower extremity edema, pleuritic chest pain, increased shortness of breath and/or presyncope. Hospitalized patients should receive low-molecular-weight heparin to avoid thromboembolic complications.

Comorbidities

A hospitalization for acute decompensated heart failure is an ideal time to assess for, and optimize treatment of, comorbidities such as diabetes, anemia, and sleep apnea (see Chapter 14). The long-term cardiovascular benefits of tight glycemic control with insulin have been well documented.[154] For patients treated with oral agents, it is important to recognize that thiazolidinediones, which have important ancillary effects on lipid metabolism and endothelial function,[155] may increase fluid retention and exacerbate heart failure, and that this effect is exacerbated by concomitant administration of insulin. In addition, metformin, another popular insulin sensitizer, is associated with a low risk of life-threatening lactic acidosis and is contraindicated in patients with heart failure. Anemia is also common in patients with advanced heart failure and is associated with increased morbidity and mortality rates.[156] Pilot studies suggest that correction of anemia with erythropoietic agents improves symptoms and functional status and may reduce readmission rates in heart failure.[157] However, definitive data on the balance of risks and benefits of anemia treatment await completion of large randomized trials.

Mechanical Cardiac Assist

For patients with severe hemodynamic compromise who do not respond to positive inotropic agents, urgent consideration should be given to support with an intra-aortic balloon pump or ventricular assist device. In the setting of cardiogenic shock complicating acute myocardial infarction, intra-aortic balloon counterpulsation (IABP) is commonly used to reduce ischemia and improve hemodynamics while awaiting more definitive treatment (e.g., percutaneous or surgical revascularization or repair of a mechanical complication such as papillary muscle rupture or ventricular septal defect). In addition, IABP may support a patient while waiting for spontaneous recovery of stunned myocardium. Absolute contraindications to intra-aortic balloon counterpulsation include aortic insufficiency and aortic dissection. Significant peripheral arterial disease involving the abdominal aorta or iliofemoral arteries is also a contraindication. For further discussion of the use of balloon counterpulsation in the setting of acute myocardial infarction, including insertion technique, monitoring, and complications, see Chapter 11 and Appendix 3.

In patients with advanced heart failure due to ischemic or nonischemic cardiomyopathy, IABP has also been used successively as a "bridge" to ventricular assist device or cardiac transplantation.[158] In this setting, systemic perfusion may be maintained and end-organ function preserved while awaiting a donor heart. However, given the increase in waiting list times in many regions, IABP is not a feasible method of providing prolonged support (i.e., weeks to months) and precludes pretransplant rehabilitation. Ventricular assist devices offer the best alternative for extended circulatory support, allowing for physical rehabilitation and reversal of renal and hepatic dysfunction before transplantation,[159] or rarely, myocardial recovery.[160] Ventricular assist devices have also been approved for permanent ("destination") therapy in select patients who are ineligible for cardiac transplant due to age or comorbidites.[161] General indications and surgical techniques for left ventricular (LVAD) or biventricular assist device (BIVAD) implantation, and perioperative care of VAD patients are discussed in Chapter 18 and Appendix 3. Decisions regarding the use of mechanical cardiac support should be made in consultation with a heart failure/transplant cardiologist and a VAD/transplant surgeon.

SPECIAL CONSIDERATIONS

Acute Heart Failure

The principles described earlier have been developed primarily to treat acute decompensation of chronic heart failure. Similar principles apply to acute heart failure, with some special considerations. Unlike the approach to an exacerbation of chronic heart failure, the primary goal of therapy for acute heart failure is temporary stabilization of the patient until definitive mechanical intervention or spontaneous recovery can occur. The design of an effective oral regimen for outpatient stabilization is not a major goal.

Heart failure in the setting of acute myocardial infarction can develop and progress rapidly, and the patient may suffer from intense precordial pain. Unless cardiogenic shock is present, arterial pressure is usually elevated due to adrener-

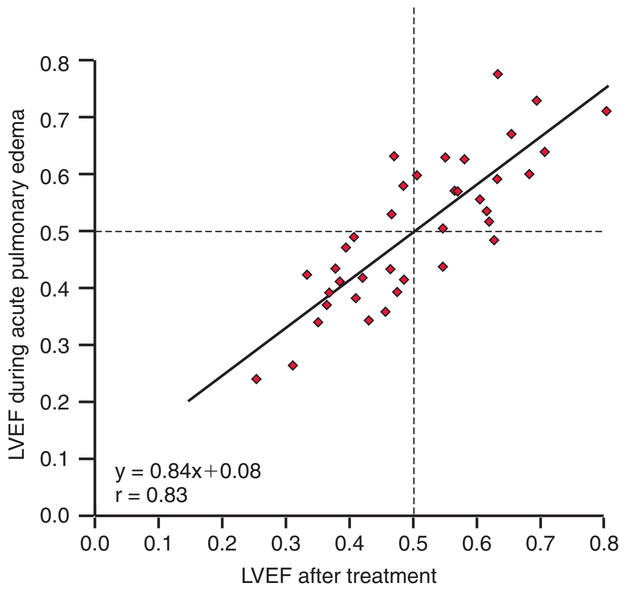


Figure 17–8 Relation between left ventricular ejection fraction (LVEF) during acute pulmonary edema and 1 to 3 days following treatment in 38 patients (14 men and 24 women, age 67 ± 13 years). *Dotted lines* indicate normal values for LVEF. (Adapted from Gandhi SK, Powers JC, Nomeir AM, et al: The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17.)

gically mediated vasoconstriction, and it may be suspected incorrectly that the pulmonary edema is due to hypertensive heart disease. However, hypertensive crises are now uncommon,[162] and funduscopic examination will usually indicate whether or not hypertensive heart disease is actually present. In addition, echocardiography may be useful in defining the pathogenesis of acute pulmonary edema. In most patients with hypertensive pulmonary edema and normal left ventricular function, the edema is due to an exacerbation of diastolic dysfunction, rather than to transient systolic dysfunction, myocardial ischemia, or severe mitral regurgitation (Fig. 17–8).[163]

Diagnosis of cardiogenic shock complicating acute myocardial infarction is occasionally delayed when blood pressure is maintained by sinus tachycardia. Intravenous inotropic support should not be postponed because of concern about increasing myocardial oxygen demand, which is also raised by increased ventricular filling pressures. Dobutamine can be initiated while a pulmonary artery catheter is being placed to monitor loading conditions and response to therapy. In contrast to the hemodynamic goals in the chronically dilated heart, low systemic blood pressure and reduced cardiac output may be less well tolerated in patients with previously normal hemodynamics, and higher filling pressures may be required to maximize cardiac output. In the setting of marked hypotension, dopamine should be initiated to support a systolic blood pressure >80 mm Hg.

Sublingual followed by intravenous nitroglycerin can be used to decrease ischemia and associated symptoms, and may also provide arterial vasodilation when the SVR is high. If symptoms are not immediately relieved with nitroglycerin, morphine sulfate given intravenously may be effective. Nitroprusside has the potential to cause a "coronary steal" in the setting of acute ischemia and should be avoided except in patients with severe hypertension. As total body volume status is usually normal, diuretics are infrequently needed during acute infarction except as initial therapy for pulmonary edema. IABP should be considered if cardiac output is markedly reduced, filling pres-sures are severely elevated, or there is evidence of ongoing ischemia. Evaluation for definitive intervention such as revascularization should not be delayed by prolonged attempts to stabilize a patient on pharmacologic therapy. In a landmark trial of cardiogenic shock complicating acute myocardial infarction, overall mortality at 30 days did not differ between patients randomized either to emergency revascularization or to initial medical stabilization; although 6-month mortality was lower in the revascularization group (50% versus 63%, $P = 0.027$).[164]

Patients with acute heart failure secondary to new mitral or aortic valve regurgitation (e.g., due to acute bacterial endocarditis) are exquisitely sensitive to afterload reduction. Arterial vasodilation with intravenous nitroprusside, followed by oral vasodilators, often improves forward flow markedly[165] and allows for elective consideration of valve replacement. Nitroprusside has also been used successfully to stabilize critically ill patients with severe aortic stenosis and left ventricular dysfunction (Fig. 17–9) while awaiting definitive aortic valve surgery.[166]

The evaluation and management of patients with acute myocarditis are discussed in Chapter 14. Lieberman and associates[167] classified myocarditis as fulminant, acute (nonfulminant), chronic active, or chronic persistent on the basis of clinicopathologic criteria. Patients with fulminant myocarditis display the least delay between initial viral symptoms and the onset of heart failure and present with severe hemodynamic compromise. However, they are more likely to recover left ventricular function and have an excellent long-term prognosis.[168] When this distinct clinical entity is suspected and confirmed by endomyocardial biopsy, aggressive hemodynamic support, including the use of inotropic agents and mechanical cardiac assist, is warranted to "bridge" patients to recovery. One exception is giant cell myocarditis in which patients are unlikely to recover even with adjuvant immunosuppressive therapy and should be considered for urgent cardiac transplantation.[169]

Heart Failure with Preserved Systolic Function

The pathophysiology of heart failure with preserved systolic function is discussed earlier, in Chapter 14, and other reviews.[18,19] Common precipitants of acute decompensation include ischemia, hypertension, and volume overload, all of which should be treated aggressively. Although cardiac output may be reduced, intravenous inotropic agents are seldom necessary to maintain vital organ perfusion and may exacerbate tachycardia or arrhythmias. Low-dose dopamine therapy (2 to 3 mcg/kg/minute) may help with diuresis in some cases. Systemic hypertension is a common target of therapy and vasodilators, often used in combination, can be adjusted without the need for hemodynamic monitoring. ACE inhibitors, angiotensin receptor blockers, and calcium channel

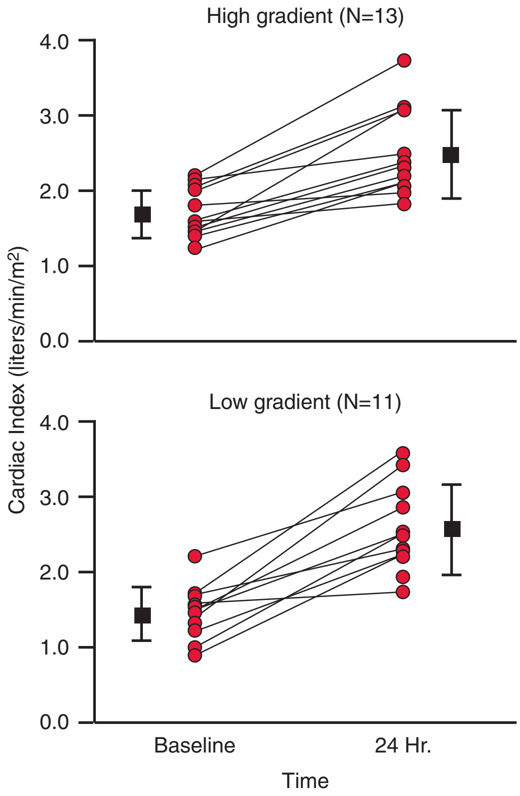


Figure 17–9 Change in cardiac index 24 hours after the start of nitroprusside infusion in subgroups of patients with left ventricular dysfunction and severe aortic stenosis according to the mean aortic-valve pressure gradient at baseline (≤30 mm Hg [low gradient] vs. >30 mm Hg [high gradient], *P* = 0.20). (Adapted from Khot UN, Novaro GM, Popovic ZB, et al: Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. N Engl J Med 2003;348:1756.)

blockers can lower blood pressure and improve ventricular compliance. Oral, topical, or intravenous nitrates may be used to reduce ventricular filling pressures and improve exertional tolerance, as well as to treat myocardial ischemia. In some patients, however, postural hypotension may limit the use of nitrates or other vasodilators.

In addition to the management of blood pressure and fluid status, heart rate control is central to preventing or treating ischemia associated with diastolic heart failure. β-Blockers and calcium channel blockers are useful negative chronotropic agents. For patients who present with new onset atrial arrhythmias, restoration of sinus rhythm is important for achieving adequate cardiac output. While awaiting therapeutic anticoagulation, β-blockers, calcium channel blockers, or digoxin may be used to control the ventricular response. For patients with a contraindication to chronic anticoagulation, a transesophageal echocardiogram should be performed before cardioversion to assess for intracardiac thrombus.[136] Electrical or chemical cardioversion should also be considered for patients with chronic heart failure and atrial fibrillation in whom adequate rate control cannot be achieved. Alternatively, ablation of the atrioventricular junction with back-up ventricular pacing may be considered.

FUTURE DIRECTIONS

The most recently approved vasoactive agent for the treatment of acute decompensated heart failure was nesiritide in 2001; however, initial enthusiasm has been tempered by concerns for renal injury[91] and mortality,[170] which may be related to excess vasodilation at higher doses. Given the potential toxicity associated with positive inotropic agents[90] and the increased recognition of the cardiorenal syndrome contributing to adverse outcomes, clinical investigations have focused on the development of alternative vasodilators and renal protective agents.

As discussed earlier, plasma levels of arginine vasopressin are elevated in patients with chronic heart failure, and correlate with poor outcomes.[24] Adverse effects of vasopressin are mediated by V_{1a} receptors in the vasculature and myocardium causing vasoconstriction and positive inotropy, respectively, and V_2 receptors in the kidney causing water retention. Vasopressin receptor antagonists are a novel class of cardiovascular agents that are being developed to attenuate disease progression and improve survival in heart failure.[24,171] In patients with advanced heart failure, conivaptan, a combined V_{1a}/V_2-receptor antagonist reduced PCWP and right atrial pressure and caused a dose-dependent increase in urine output.[172] Tolvaptan is an oral selective V_2-receptor antagonist that has been shown to increase urine volume and decrease body weight compared with placebo in patients with acute decompensated heart failure, while increasing serum sodium concentrations in hyponatremic patients.[173] Whether this novel class of agents will offer additional clinical benefits with less adverse effects when compared with currently available drugs remains to be determined.

Another neurotransmitter that is activated in the kidney in patients with heart failure and may serve as a local target for therapy is adenosine. Adenosine stimulates A_1-receptors in afferent arterioles and proximal and distal tubules causing local constriction and sodium reabsorption, respectively. In addition, A_1-receptors in the macula densa mediate reduction in glomerular filtration rate via tubuloglomerular feedback. In patients with chronic heart failure, selective A_1-receptor antagonists enhance urine output and attenuate the decrease in glomerular filtration rate caused by loop diuretics.[174] Current studies are ongoing to test the safety and efficacy of adenosine receptor antagonists in patients with acute decompensated heart failure and diuretic resistance.

A limitation of most positive inotropic agents (e.g., dobutamine, milrinone) is that they act by increasing intracellular calcium in the myocyte, and may cause tachycardia and arrhythmias. Levosimendan is a pyridazinone-dinitrile derivative that enhances calcium sensitivity of myofilaments via calcium-dependent binding to troponin C.[175] Other pharmacologic actions include mild phosphodiesterase inhibition and activation of potassium channels. In patients with moderate-to-severe heart failure due to ischemic or nonischemic cardiomyopathy, a 6-hour infusion of levosimendan caused rapid, dose-dependent increases in stroke volume and cardiac index, and decreases in PCWP and right atrial pressure with only a modest increase in heart rate.[176] Levosimendan was well tolerated and appeared to improve symptoms without proarrhythmia. However, additional phase II data[177] and preliminary results of two large randomized studies[178] suggest that hypotension and tachyarrhythmias may

limit the use of levosimendan in patients with acute decompensated heart failure.

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Chapter 18

Cardiac Transplantation and Circulatory Support Devices

Michael A. Mathier and Srinivas Murali

CHAPTER CONTENTS

Despite treatment with new drug regimens and high-risk cardiac surgery, many patients with heart failure (HF) progress to advanced stages characterized by marked symptomatic limitation and profound hemodynamic compromise. Cardiac transplantation is the first line therapy for select patients with end-stage HF. In the United States, there are 135 transplant centers performing approximately 2000 procedures annually. Unfortunately, the limited supply of donor hearts has restricted the growth of cardiac transplantation and has led to the search for alternative strategies such as mechanical circulatory support. The recent explosion in mechanical circulatory support technology offers the promise of a universally available therapy to decrease morbidity and mortality rates in all patients with end-stage HF.

CARDIAC TRANSPLANTATION

Human cardiac transplantation was first performed in 1967. Over the subsequent 4 decades, cardiac transplantation evolved into the gold standard therapy for many patients with end-stage HF. This evolution has been made possible by significant advances in every aspect of cardiac transplantation: recipient and donor selection and management, organ preservation, surgical technique, immunosuppression, and management of acute and chronic post-transplantation complications. Approximately 3000 cardiac transplantations are performed worldwide each year. The 1-, 5-, and 10-year survival rates post-cardiac transplantation are approximately 83%, 73%, and 68%, respectively. Long-term survival (more than 15 years) is not uncommon, largely as a result of more limited and targeted immunosuppression. The total number of cardiac transplantations performed annually has held steady for the past 20 years, largely owing to limited donor availability.[1,2]

During this same period, dramatic advances have been made in the medical and nontransplant surgical therapy of patients with advanced HF. Comprehensive pharmacotherapy has significantly delayed the progression of HF to its advanced stages. Biventricular pacemakers and implantable cardioverter-defibrillators have contributed importantly to reductions in the rates of HF morbidity and mortality. In addition, surgical advances have allowed the benefits of coronary revascularization and valvular repair to be extended to patients with poor ventricular function. Nevertheless, cardiac transplantation remains the best option for many patients with advanced HF.

Patient Selection

Although cardiac transplantation offers excellent patient outcomes, it has several important limitations. Among these are inadequate donor availability, significant perioperative risk, and substantial post-transplantation morbidity and mortality. Consequently, optimizing patient selection for the procedure is critical. The overriding principle is to select patients whose cardiac dysfunction substantially impairs their lifestyle and threatens their life span, but who do not have sufficient extracardiac comorbidities to importantly compromise post-transplant outcome. Individual transplant programs establish their own inclusion and exclusion criteria; a representative list of criteria is shown in Table 18–1.[3]

Cardiac transplantation is most commonly performed for chronic severe left ventricular systolic dysfunction, although it is occasionally used in patients with other advanced cardiac pathology (e.g., coronary artery disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or others). A standard array of cardiac tests is generally performed to thoroughly assess each patient's cardiac status. The goals of cardiac testing are to determine that

1. The cardiac disease limits functional status or anticipated survival to a degree sufficient to warrant consideration of transplantation;
2. There are no acceptable alternative therapies (medical or surgical) for the cardiac disease;
3. Irreversible pulmonary hypertension is not present; and
4. Appropriate therapy is chosen to "bridge" the patient to transplantation.

Assessment of Cardiac Disease Severity

The assessment of the severity of the cardiac disease is based on anatomic, functional, and hemodynamic data. The functional assessment includes a determination of NYHA class, as well as more objective measures of exercise capacity such as peak oxygen consumption or 6-minute walk distance. Peak oxygen consumption ($\dot{V}O_2$) is measured by breath-to-breath respiratory gas analysis during either bicycle ergometry or

Table 18–1 Selection Criteria for Cardiac Transplantation Candidates

Inclusion Criteria

- Advanced heart failure with severe refractory symptoms and markedly shortened life expectancy
- Advanced coronary artery disease with refractory angina not amenable to revascularization
- Malignant ventricular arrhythmias unresponsive to standard therapies

Exclusion Criteria

- Advanced age
- Irreversible pulmonary hypertension
- Chronic noncardiac illness compromising survival and functional recovery
- Severe peripheral vascular disease
- Morbid obesity (BMI ≥ 40 kg/m^2)
- Active or recent malignancy
- Active infection (excluding chronic driveline infections of mechanical circulatory support devices)
- Human immunodeficiency virus seroconversion
- Drug, tobacco, or alcohol abuse within the past 6 months
- Psychiatric or psychosocial instability

BMI, body mass index.

graded treadmill exercise. In a seminal study, peak $\dot{V}O_2$ was found to predict mortality in patients with advanced HF (Fig. 18–1).[4] Based on this study, a peak $\dot{V}O_2 \leq 14$ mL/kg/min is commonly used as a threshold for listing the patient for cardiac transplantation. Studies have suggested that in patients with advanced HF who are treated with β-adrenergic antagonists, this threshold may be too high, and that a lower peak $\dot{V}O_2$ may be more appropriate for transplant listing.[5] Other parameters obtained during these studies, including minute ventilation-carbon dioxide ($\dot{V}E/\dot{V}CO_2$) slope (a measure of ventilatory efficiency), have been shown to predict outcome, and may be useful in the evaluation of a patient's candidacy for cardiac transplantation.[6]

The 6-minute walk distance has been shown to correlate well with peak $\dot{V}O_2$, suggesting that this simpler measure of functional capacity can be used in place of the more cumbersome oxygen consumption study.[7] A number of readily available clinical and laboratory parameters such as hyponatremia, azotemia, anemia, and cachexia, along with dependence on inotropic support, identify patients with a poor prognosis.[8] Calculation of a risk score based on clinical variables has been advocated by some as a more refined predictor of outcome in patients with advanced HF.[9]

Assessment of the Pulmonary Vasculature

An important determinant of candidacy for cardiac transplantation is the status of the pulmonary circulation. Patients with long-standing left HF frequently develop pulmonary hypertension, which may or may not reverse with acute or chronic vasodilator therapy. Agents commonly used to assess pulmonary vasoreactivity acutely include sodium nitroprusside, prostaglandin E_1 (PGE_1), milrinone, and inhaled nitric oxide. As shown in Figure 18–2, patients with reversible

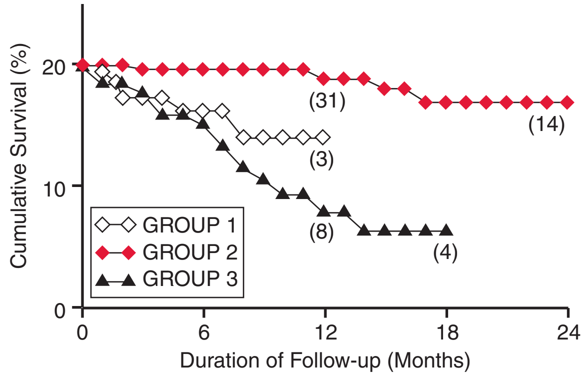


Figure 18–1 Survival curves for patients with $\dot{V}O_2$ of more than 14 mL/kg/min (group 2) and reduced $\dot{V}O_2$ (groups 1 and 3). (From Mancini D, Eisen H, Kussmaul W, et al: Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;82:778-86).

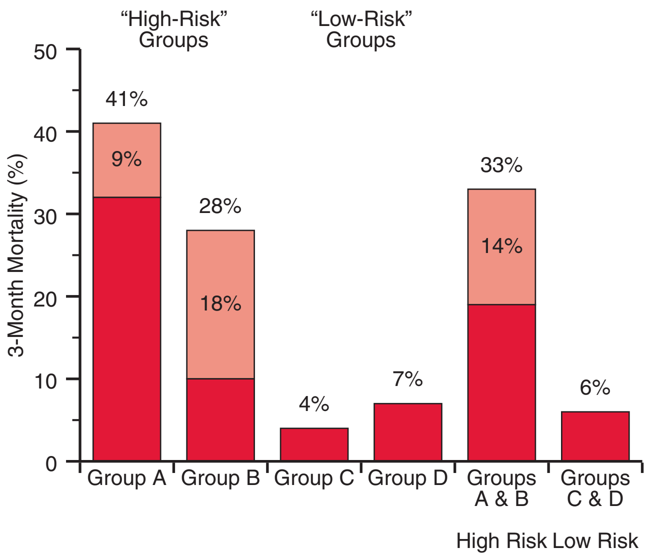


Figure 18–2 Three-month mortality after transplantation: Differentiation of low- and high-risk groups according to preoperative pulmonary hypertension. Group A = patients whose pulmonary vascular resistance could not be decreased to <2.5 Wood units (n = 32). Group B = patients whose pulmonary vascular resistance could be reduced to ≤ 2.5 Wood units at the expense of severe systemic hypotension (n = 40). Group C = patients whose pulmonary vascular resistance could be lowered to ≤2.5 Wood units without severe systemic hypotension (n = 78). Group D = patients whose pulmonary vascular resistance was <2.5 Wood units at baseline. *Light red bars,* deaths due to right heart failure and pulmonary hypertension. *Dark red bars,* deaths due to other causes. (Redrawn from Costard-Jackle A, Fowler MB: Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: Testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high-risk group. J Am Coll Cardiol 1992;19:48-54, with permission.)

pulmonary hypertension have post-transplant survival rates similar to those patients with normal pulmonary pressures prior to transplant. Patients with irreversible pulmonary hypertension have a significantly worse post-transplant survival, largely due to failure of the donor right ventricle.[10] For these patients, alternative strategies such as combined heart-lung transplantation or heterotopic heart transplantation (with retention of the native heart to take advantage of its "trained" right ventricle) may be considered.[11]

Other Cardiac Transplantation Candidacy Issues

Age

Most adult cardiac transplant programs establish an upper age cut-off of 65 years for transplant candidacy. Data from the International Society for Heart and Lung Transplantation (ISHLT) Registry have suggested that survival after cardiac transplantation declines with increasing recipient age after 50 years of age; this effect is most striking above 70 years of age.[1,2] Among the possible explanations for this association is the apparent increased risk of post-transplantation malignancy in older versus younger patients. Despite this, several reports of acceptable outcomes in an older patient population have emerged.[12,13]

Comorbidities

Many cardiac transplantation programs list significant irreversible noncardiac organ dysfunction as an exclusion criterion. Examples include intrinsic renal disease with a creatinine clearance of 40 mL/min or less, intrinsic pulmonary disease with spirometric values less than 50% of predicted, and biopsy-proven hepatic cirrhosis. There are, however, a number of reports of successful multiorgan transplantations, most commonly combined heart-kidney, heart-lung, and heart-liver transplants.[14,15] Similarly, significant noncardiac comorbidities (such as diabetes with end-organ dysfunction) may exclude patients from cardiac transplantation, although reports of acceptable outcomes in these populations exist.[16] Other relative contraindications to transplant include conditions that are likely to worsen with corticosteroid therapy—such as obesity and osteoporosis.

Table 18–2 United Network of Organ Sharing Organ Allocation System

Status	Definition
1A	Patient admitted to the listing center with: • Mechanical ventilation • Intra-aortic balloon pump • Extracorporeal membrane oxygenator • Mechanical ventricular assist device within a 30-day period or complicated by infection, thromboembolism or device malfunction • Single high-dose or multiple low-dose inotrope infusion with pulmonary artery catheter monitoring
1B	Patient on low-dose single inotrope or with uncomplicated mechanical ventricular assist device beyond 30-day period
2	Patient not meeting 1A or 1B criteria
7	Patient listed but temporarily unsuitable for cardiac transplantation

Immunologic Sensitization

Although rarely an exclusion for cardiac transplantation by itself, immunologic sensitization (the presence of antihuman leukocyte antigen [HLA] donor-specific antibodies) of potential transplant recipients can pose a significant challenge. All potential recipients undergo immunologic assessment, usually via a complement-dependent cytotoxicity assay (panel-reactive antibodies, or PRA). Because this technique is relatively insensitive, newer methods such as flow cytometry for antibody screening may be preferable.[17] Highly sensitized candidates commonly have a history of multiple pregnancies or prior transfusions, and they require careful donor selection and perioperative immunologic management as described subsequently.

Listing for Cardiac Transplantation

The United Network of Organ Sharing (UNOS) was created in 1986 by the United States Congress. UNOS oversees the allocation of organs on a nationwide basis to recipients who have been registered by transplant programs on regional waiting lists. Local Organ Procurement Organizations (OPOs) are nonprofit agencies responsible for evaluating the suitability of potential donor organs and for coordinating organ recovery, preservation, and transport to the transplant center. Organs are allocated according to ABO blood typing, size matching, duration on the waiting list, and severity of disease. In 1999, UNOS updated the criteria by which disease severity affects patient priority on the waiting list. Table 18–2 summarizes the current UNOS status criteria.

Improved success rates with cardiac transplantation have inevitably led to efforts to expand the procedure to previously excluded patient populations. One controversial strategy that has been used by some centers is the creation of a second or alternate list for those candidates deemed to be at higher risk.[18,19] Organs accepted for patients on this list are those judged to be marginal (e.g., from older donors or donors with single-vessel coronary disease), and therefore not acceptable for most candidates who meet standard listing criteria. Some have argued, however, that using suboptimal donor organs for higher risk candidates will lead to worse outcomes.

Pre-transplantation Patient Management

Patients deemed to be acceptable candidates for cardiac transplantation require careful management as they await the procedure. Standard pharmacologic (see Chapter 14) and device therapies for HF, as well as appropriate lifestyle modifications (see Chapter 13), are recommended for all patients. Patients with intractable signs and symptoms related to low cardiac output and end-organ hypoperfusion (renal or hepatic dysfunction or poor nutritional status) may require continuous inotropic therapy or mechanical cardiac support, both of which affect the priority status of the patient in the UNOS system. Patients managed with continuous intravenous inotropic therapy or mechanical cardiac support

require careful surveillance for, and aggressive therapy of, infection. Similarly, patients with evidence of pulmonary hypertension require careful follow-up of their pulmonary pressures. Chronic left ventricular unloading with mechanical circulatory support may prevent worsening of, or even reverse previously refractory, pulmonary hypertension and allow for successful transplantation.[20]

Patients found to be highly immunologically sensitized may benefit from immunomodulatory therapy before undergoing cardiac transplantation. Numerous protocols have been described in the literature, including those that use immunoglobulin and plasmapheresis.[21,22] These protocols aim to reduce the patient's burden of preformed antibodies to commonly encountered antigens, both to increase the possibility (and shorten the waiting time) of finding a donor with a negative prospective cross match, and to decrease the chance of rejection of the transplanted heart.

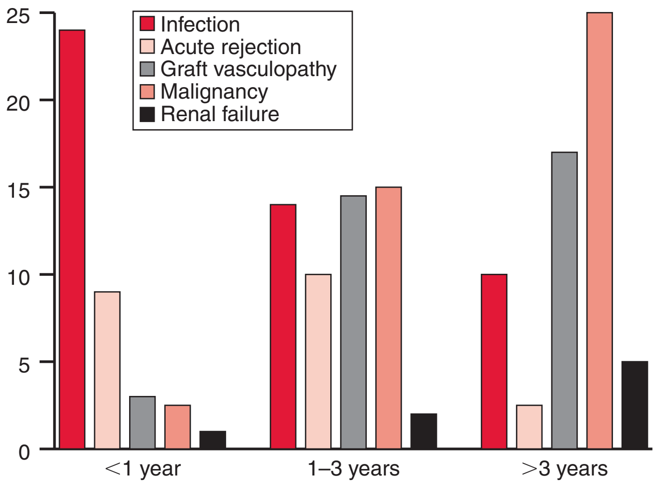


Figure 18–3 Frequency of various causes of death over time in patients following cardiac transplantation. (Redrawn from Mathier MA, McNamara DM: Management of the patient after heart transplant. Curr Treat Options Cardiovasc Med 6:459-69, 2004, with permission.)

Cardiac Transplantation Surgical Technique

The surgical technique for cardiac transplantation has remained fairly constant for the last 2 decades. One significant modification has been the adoption of a bicaval anastomotic technique in place of the standard biatrial anastomosis. With both techniques, the donor left atrium is anastomosed to a retained cuff of recipient left atrium with the pulmonary veins left intact. In the bicaval technique, the donor and recipient vena cavae are anastomosed after complete excision of the recipient right atrium. Studies indicate that the bicaval technique results in improved atrial function and decreased incidence of atrial arrhythmias.[23,24] A further modification, termed *total orthotopic cardiac transplantation*, combines a bicaval anastomosis with pulmonary vein anastomoses. This technique has not as yet been shown to offer significant benefit over biatrial or bicaval techniques.[25]

Advances have also been made in the area of organ preservation after harvest.[26] This may have contributed to the observation that outcomes with longer donor ischemic times are not markedly worse compared with those with shorter ischemic times.[27] In addition, immediate postoperative management has improved with the judicious use of inotropic agents, acute pulmonary vasodilators, and even temporary mechanical cardiac support for instances of transient allograft dysfunction related to ischemia, elevated pulmonary pressures, or both.[28-30]

Management of the Patient After Cardiac Transplantation

The management of the patient after cardiac transplantation involves three main strategies (1) optimization of immunosuppressive therapy; (2) prevention of allograft rejection and complications resulting from the transplant or the immunosuppressive agents; and (3) treatment of allograft rejection and associated complications when they arise. The relative impact of these various conditions on mortality rates varies over time after cardiac transplantation (Fig. 18–3).[31]

Acute cellular rejection is an important cause of morbidity and mortality in patients post-cardiac transplantation. Despite intensive investigation of potential noninvasive indicators of rejection, transvenous endomyocardial biopsy remains the diagnostic tool of choice, and revised ISHLT criteria have been published (Table 18–3).[32] Of note, however, a completed multicenter study suggested that peripheral blood gene expression profiling of circulating leukocytes may be able to identify patients for whom it is safe to defer endomyocardial biopsy.[33] The risk of acute cellular rejection is highest in the first year post-cardiac transplantation and declines significantly thereafter. This observation underlies the strategy of more intensive immunosuppression and surveillance for rejection early after transplant—with a gradual decrease in both over time (Table 18–4). The incidence of infection similarly is higher in the months following transplantation and declines thereafter. Accordingly, prophylaxis against opportunistic infections is of greatest usefulness early after transplantation, when the level of immunosuppression is highest.[34,35]

Over time, after cardiac transplantation, other conditions assume greater importance in determining patient outcome. Hypertension, diabetes, and dyslipidemia are quite common, occurring in 73%, 24%, and 50% of patients within the first year after cardiac transplantation, respectively.[1] The high incidence of these conditions reflects the fact that they are frequent comorbidities in patients who require transplantation and that immunosuppressive therapy can cause or exacerbate these conditions. Aggressive therapy of each is recommended, although data indicating that this improves outcomes in patients following cardiac transplantation are limited.[36] Among the important sequelae that may be prevented or delayed with such therapy are cardiac allograft vasculopathy (CAV) and renal insufficiency. Late mortality post-cardiac transplantation is predominantly related to CAV, renal failure, and malignancy.[2]

Prevention and Treatment of Cardiac Rejection

The primary management goal of immunosuppressive therapy is to limit episodes of acute rejection. To accomplish this in the perioperative period, some programs continue to

Table 18–3 ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection*

2004		1990	
Grade 0 R†	No rejection	Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage	Grade 1, mild A—Focal B—Diffuse	Focal perivascular and/or interstitial infiltrate without myocyte damage Diffuse infiltrate without myocyte damage
		Grade 2 moderate (focal)	One focus of infiltrate with associated myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 3, moderate A—Focal B—Diffuse	Multifocal infiltrate with myocyte damage Diffuse infiltrate with myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage, ± vasculitis	Grade 4, severe	Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage + vasculitis

*The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required.
†Where "R" denotes revised grade to avoid confusion with 1990 scheme.
ISHLT, International Society for Heart and Lung Transplantation.

Table 18–4 Frequency of Follow-Up Evaluations Following Cardiac Transplantation

	Discharge to Week 4	Month 1 to Month 3	Month 4 to Year 1	Year 1 to Year 5	After Year 5
Office visit	q 1 week	q 2 weeks	q 1-2 months	q 3-6 months	q 6 months-1 year
Blood work	q 1 week	q 2 weeks	q 1-2 months	q 3 months	q 3 months
Right Heart Catheterization and Biopsy	q 1 week	q 2 weeks	q 1-2 months	q 3 months-1 year	As needed
Echocardiogram	As needed	At month 3	q 3 months	q 6 months-1 year	As needed
DSE	—	—	At year 1	q 1 year	q 1 year
Coronary Angiogram	—	—	At year 1	q 2 years	As needed

Blood work includes: serum chemistries; complete blood count; liver function testing; serum levels of calcineurin inhibitor and sirolimus; lipid profile, glycosylated hemoglobin; uric acid; thyroid studies less frequently.
DSE, dobutamine stress echocardiogram.
From Mathier MA, McNamara DM: Management of the patient after heart transplant. Curr Treat Options Cardiovasc Med 2004;6:459-69, with permission.

use induction immunosuppression with lymphocytolytic therapy or daclizumab, a humanized monoclonal antibody against the interleukin-2 (IL-2) receptor. This strategy may be effective,[37,38] but may carry increased risk of infection and malignancy.[39,40] Many U.S. transplantation programs avoid induction immunosuppression in most patients, relying instead on a standard three-drug regimen (calcineurin inhibitor, corticosteroid, and antimetabolite; see later) from the time of the transplantation. The risk of rejection is at its maximum during the initial period of exposure to the allograft, and consequently the level of immunosuppression is maintained at its highest level during the first 6 months post-transplant. For long-term survival, limiting the complications of immunosuppression is of primary importance and leads to a critical additional management goal: to limit rejection with the lowest level of immunosuppression possible.

Calcineurin Inhibitors

Cyclosporine, or cyclosporine A (CsA), is a cyclic polypeptide calcineurin inhibitor that decreases transcription and secretion of IL-2 and other cytokines, and prevents T helper cell activation. The introduction of CsA in the 1980s led to a marked reduction in acute rejection and significant improvement in survival after cardiac transplantation. Initial target trough levels are 200 to 300 ng/mL for the first 6 months post-transplant, and 100 to 250 ng/mL thereafter. The main side effects of CsA are hypertension, peripheral neuropathy, nephrotoxicity, hirsutism, and gingival hyperplasia. CsA is metabolized by the cytochrome P-450 system; numerous drugs that inhibit or induce this system are well known to increase (e.g., diltiazem, allopurinol, amiodarone) or decrease (e.g., nafcillin, phenobarbital, phenytoin) CsA levels. Target

levels are usually somewhat lower in older recipients given their more modest immune activation and greater risk of malignancies, renal dysfunction, and infection.

Tacrolimus (FK506) is a macrolide immunosuppressive agent that acts with a similar mechanism, but may be more potent than CsA. Although a randomized evaluation of CsA-versus tacrolimus-based regimens did not demonstrate a survival difference, tacrolimus appeared to have a potentially better side-effect profile, with less hypertension and dyslipidemia but more glucose intolerance.[41] Most centers still use a CsA-based regimen, reserving tacrolimus as alternative therapy for subjects with multiple rejection episodes on CsA, but others have opted for routine tacrolimus-based therapy. Initial target levels are 15 to 20 ng/mL for the first 6 months, and 10 to 12 ng/mL thereafter.

Corticosteroids

Corticosteroids remain a central part of immunosuppressive therapy during the first 12 to 24 months post-transplant and are the most commonly used agent for the therapy of acute rejection. Among the many mechanisms of action of corticosteroids are suppression of IL-1 and IL-2 synthesis and macrophage function. At most institutions, intravenous methylprednisolone (500 mg IV intraoperatively, then tapering to 20 mg IV twice a day over the first 5 post-operative days) is used initially, then converted to oral prednisone (20 to 30 mg PO every day), which is then slowly tapered over the subsequent 12 to 24 months. Each reduction in the prednisone dose is generally followed by a biopsy within 2 to 3 weeks to ensure the reduction has not resulted in cellular rejection. When acute cellular rejection occurs, an oral or intravenous "pulse" of corticosteroids (e.g., 1 gm IV every day for 3 days) is commonly used as primary therapy for the rejection episode. It is crucial that corticosteroid use be minimized to avoid long-term complications, including glucose intolerance, osteopenia, skeletal myopathy, hypertension, and cataracts. In light of this, there has been increasing interest in completely corticosteroid-free immunosuppressive regimens; however, the safety and efficacy of this strategy remain under investigation.[42]

Antimetabolites

Before the introduction of CsA in the 1980s, standard immunosuppressive therapy consisted of corticosteroids and azathioprine (2 to 3 mg/kg PO every day), an antimetabolite that inhibits purine biosynthesis and limits lymphocyte proliferation. Azathioprine is an important part of standard three-drug therapy in many centers, although its use has decreased with the advent of mycophenolate mofetil (MMF; generally given at 1000 to 1500 mg PO twice a day). Although MMF also inhibits purine synthesis, its selectivity for lymphocytes results in less frequent bone marrow suppression, although regular monitoring of white blood cell counts is necessary. In a randomized trial comparing the two agents in combination with a calcineurin inhibitor and corticosteroids, MMF was superior to azathioprine in decreasing both the frequency and severity of cardiac allograft rejection.[43] This led most centers to replace azathioprine with MMF for standard immunosuppressive therapy. Gastrointestinal side effects are common with MMF, often necessitating a dosage decrease.

Sirolimus

Sirolimus, or rapamycin, acts via the TOR (target of rapamycin) receptor to inhibit lymphocyte activation and proliferation in response to antigenic and cytokine stimulation. Its mechanism is distinct from other immunosuppressive agents. It has been shown to slow the progression of CAV in a single-center randomized trial when used in combination with a calcineurin inhibitor.[44] In native (nontransplant) coronary artery disease, sirolimus-eluting stents have been shown to have lower rates of restenosis, presumably by a similar antiproliferative mechanism (see Chapter 7). Sirolimus (2 to 5 mg PO every day, adjusted to achieve trough levels of 5 to 7 mg/mL) is sometimes used in place of calcineurin inhibitors as a renal sparing agent. Marked dyslipidemia may be seen with sirolimus therapy. Everolimus, a derivative of sirolimus with similar antiproliferative effects, may prevent the development of CAV.[45]

Lymphocytolytic Agents

Severe acute cardiac allograft rejection refractory to corticosteroids and intensification of standard immunosuppression may be treated with cytolytic agents. Examples include rabbit antithymocyte globulin or OKT3 (anti-CD3 monoclonal antibody). Cytolytic therapy produces profound immunosuppression via rapid depletion of circulating T lymphocytes. Patients who undergo such treatment must be monitored carefully for severe leukopenia and opportunistic infection and generally require supportive care to treat symptoms of a cytokine-release syndrome.

Prevention and Treatment of Post-transplant Complications

The major complications that occur following cardiac transplantation include infection, hypertension, diabetes, dyslipidemia, osteoporosis, CAV, renal insufficiency, and malignancy. Preventive efforts focus on infection (prophylactic anti-pneumocystis and antiviral therapy), osteoporosis (minimization of corticosteroid use and calcium supplementation), CAV (management of standard cardiac risk factors and minimization of rejection), renal insufficiency (minimization or alternative choice of immunosuppression), and malignancy (minimization of immunosuppression).

Opportunistic Infections

Opportunistic infections occur with the greatest frequency in the first several months after cardiac transplantation. The opportunistic infections targeted with prophylactic strategy in this period are herpesviruses, most notably cytomegalovirus (CMV), *Pneumocystis carinii* pneumonia, and oropharyngeal candidiasis.

The risk of viral opportunistic infection is related to the intensity and type of immunosuppression and the viral status of both the donor and the recipient. A recipient without prior CMV exposure who receives a heart from a CMV-positive donor has a 50% to 75% risk of developing CMV disease; a recipient with prior CMV exposure has a 10% to 15% chance, regardless of donor status.[46] Patients at high risk for CMV disease generally receive ganciclovir prophylaxis (typically

5 mg/kg IV twice daily for 14 days followed by 5 mg/kg IV every day for 14 more days or 1000 mg PO three times a day for 2 to 3 months). Those at lower risk can receive oral valacyclovir prophylaxis or rely on a preemptive treatment strategy without prophylaxis.[47,48] CMV disease is notorious for nonspecific symptoms and findings: the clinical presentation can range from a mild influenza-like illness to life-threatening pneumonitis or enteritis. Therefore, a high index of suspicion for CMV is required when evaluating constitutional, respiratory, or gastrointestinal complaints.

Pneumocystis carinii pneumonia is infrequently seen with current prophylactic strategies. The risk of this disease is greatest during the period of highest corticosteroid dosing, prompting the use of prophylactic trimethoprim-sulfamethoxazole (single-strength [80/400 mg] tablet PO every day) for the first 6 to 12 months, with less frequent dosing or discontinuation thereafter. This agent also appears to be effective against a variety of other pathogens, including toxoplasmosis, *Listeria*, and urinary tract pathogens.[47] Dapsone may be an acceptable alternative in patients with sulfa allergy, or who develop renal insufficiency or hyperkalemia on trimethoprim-sulfamethoxazole.

Nystatin liquid or mycostatin troches are usually effective in preventing oropharyngeal candidiasis. Although these represent the most common targets for antibiotic prophylaxis in patients following cardiac transplantation, many other opportunistic and nonopportunistic infections can occur.[47] A high index of suspicion for opportunistic infections is required. A full discussion of the therapy of established infections is beyond the scope of this chapter.[49]

Hypertension

Hypertension occurs frequently in cardiac transplant recipients; the incidence in long-term follow-up has been reported to be over 70% at 1 year and as much as 95% at 5 years. Hypertension after cardiac transplantation may have several etiologies, including preexisting essential hypertension, chronic use of calcineurin-inhibitors, chronic kidney disease, and alterations in renin-angiotensin-aldosterone system function.[50] Abnormalities in endothelial function have also been postulated to play a role; treatment of patients with omega-3 fatty acids preserves endothelial function and prevents increases in arterial pressure.[51]

Most standard antihypertensive agents are safe and are likely to be effective in patients following cardiac transplantation. A randomized comparison of diltiazem and lisinopril in hypertensive transplant patients found both agents to be safe, but neither to consistently provide adequate pressure control when used as monotherapy.[52] Diltiazem may have the ancillary benefits of raising CsA levels and, in one study, of slowing the development of CAV.[53] In practice, multidrug regimens for the control of hypertension are common, often including adrenergic antagonists such as β-blockers or clonidine. A thorough understanding of potential drug interactions is mandatory.

Diabetes

Cardiac transplantation in patients with diabetes at the time of surgery appears to offer a similar outcome as compared with patients without pretransplant diabetes.[54] In the first year after cardiac transplantation, however, preexisting diabetes frequently becomes much more difficult to treat. In addition, many patients will develop diabetes for the first time during this period, primarily as a result of corticosteroid therapy. Diabetes often requires therapy only during the period of corticosteroid administration. Either oral agents or insulin may be effective in the treatment of transplant-related diabetes.[55] Metformin is generally avoided because of concerns over renal dysfunction. Consensus guidelines for the management of diabetes in transplant recipients have been published.[56]

Dyslipidemia

Dyslipidemia develops in 50% of patients at 1 year and over 80% at 5 years. Dyslipidemia appears to be more severe in patients treated with CsA as compared with tacrolimus; fewer patients treated with tacrolimus require lipid-lowering therapy.[41,57] A small, randomized trial in patients with post-transplant dyslipidemia comparing simvastatin, gemfibrozil, and cholestyramine demonstrated superior total and LDL cholesterol-lowering effects for simvastatin. Gemfibrozil improved triglyceride levels.[58] A larger, longer-term randomized trial of simvastatin started early after heart transplantation versus dietary therapy alone revealed significant reduction in mortality, rates of CAV, and severe rejection without significant adverse effects in the simvastatin group.[59] This and other studies suggest that statins may have independent beneficial immunomodulatory effects. A head-to-head nonrandomized comparison of simvastatin and pravastatin suggested greater safety and efficacy of pravastatin.[60] Atorvastatin appears to be safe and effective in the treatment of dyslipidemia in the transplant patient.[61] Accordingly, pravastatin and atorvastatin are the generally preferred agents. There appears to be some increased risk of myositis and rhabdomyolysis with statin use in patients following cardiac transplantation, necessitating heightened clinical surveillance for such complications when using higher doses or combinations of agents.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is now the most common cause of late allograft dysfunction and death in patients following cardiac transplantation.[1] Risk factors for the development of CAV include frequency and severity of cellular rejection,[62] smoking, dyslipidemia, diabetes, antecedent coronary artery disease in either the recipient or donor, and older age of either the recipient or donor.[63] Studies indicate a potential role of systemic inflammation and infectious agents in the development of CAV.[64] CAV is associated with both worse functional status[65] and worse survival,[66,67] with late manifestations including refractory HF and sudden cardiac death. Most patients who have undergone cardiac transplantation lack an adequate anginal mechanism, necessitating a regular screening strategy. Intravascular ultrasound is the most sensitive diagnostic test for the detection of graft coronary disease. Standard coronary angiography, radionuclide perfusion imaging, and dobutamine stress echocardiography are frequently used (see Table 18–4). CAV may be a diffuse, concentric, and often distal process that is not amenable to percutaneous or surgical revascularization. On occasion, how-

ever, it may manifest as discrete, proximal stenoses treatable by standard revascularization techniques.

Medical therapy of CAV generally includes the use of diltiazem and a statin. Antioxidant vitamins may also delay early progression of CAV.[68] The mechanisms by which statins prevent the development and slow the progression of CAV are not fully understood. In addition to beneficial effects on serum lipid levels, statins preserve coronary endothelial function and modulate the elaboration of pro-inflammatory cytokines in the transplanted heart.[69] When combined with CsA, corticosteroids and statins, everolimus decreased the incidence of CAV within the first year after cardiac transplantation as compared with azathioprine added to the same combination.[45] In patients with established CAV, substituting sirolimus for azathioprine or MMF (in combination with corticosteroids and a calcineurin inhibitor) resulted in a significant decrease in disease progression.[44] Coronary angioplasty,[66,67] stenting,[70] and intracoronary brachytherapy[71] have all been used with acceptable results in the treatment of CAV. In addition, standard, off-pump[72] and minimally-invasive coronary artery bypass grafting[73] have been successfully performed in highly select patients who have undergone cardiac transplantation. Retransplantation for CAV appears to have greater success than when it is employed for acute graft failure or acute cellular rejection.[74] Although the rate of early mortality following re-transplantation for CAV is comparable with that of initial transplantation, long-term survival is worse.[75]

Renal Insufficiency

The risk of renal insufficiency is related to patient age, baseline renal function, and the development of hypertension.[76,77] Estimates of the incidence of end-stage renal disease postcardiac transplantation range from 5% to 8%,[78-80] and survival in patients experiencing renal failure is significantly worse than in patients with preserved renal function.[78,79] It is generally accepted that calcineurin inhibitor use increases the risk of renal insufficiency,[78] however, the relationship between dosing of these agents and the development of renal insufficiency is still uncertain.[80,81] The conversion of patients with renal insufficiency from a calcineurin inhibitor-based immunosuppressive regimen to one based on MMF and sirolimus appears to be safe and effective and is associated with an improvement in renal function.[82,83] Hemodialysis, peritoneal dialysis, and renal transplantation have all been reported to be acceptable therapies for end-stage renal disease in cardiac transplant patients.[84]

Malignancy

The final major cause of mortality in patients after cardiac transplantation is malignancy. Although careful vigilance should be maintained for all malignancies,[85] lymphomas (Epstein-Barr virus–associated post-transplant lymphoproliferative disease [PTLD]) and skin cancers in particular[86,87] occur with increased frequency. One large study of patients after heart transplantation found an overall incidence of PTLD of 6%, and an incidence among long-term survivors of 15%.[88] In general, the risk of malignancy appears to correlate with the intensity and duration of immunosuppression. Patients exposed to induction therapy or who receive OKT3 for treatment of severe rejection are at particularly high risk. Although younger recipients of cardiac transplants may be at higher risk for PTLD,[88] older patients at the time of transplantation appear to be at significantly increased risk for non-PTLD cancers.[89] PTLD often responds to a decrease in the intensity of immunosuppression, with or without concomitant antineoplastic therapy. Disease progression can often be monitored with serial PET or CT scanning. An anti-CD20 monoclonal antibody (rituximab) has been reported to be of benefit in select cases.[90] Skin cancers developing in transplant recipients, particularly squamous or basal cell carcinomas, generally respond well to local excision; recurrence is common, however.

Future Directions

The last several decades have seen significant improvements in the management of patients before and after cardiac transplantation. One challenge for the future will be to extend the life expectancy of patients following transplantation. This will depend on our ability to prevent and treat the long-term complications of transplantation, including many of the adverse consequences of immunosuppression. Toward this end, extensive investigation is underway into possible strategies for the induction of selective immune tolerance to the allograft. If successful, such strategies would likely yield an optimal post-transplant outcome. Ongoing investigation in the field of xenotransplantation may offer the possibility of an unlimited supply of donor organs and allow for expansion of transplantation to increasing numbers of patients.

CIRCULATORY SUPPORT DEVICES

The development of circulatory assist devices began in 1964 under the direction of the Artificial Heart Program at the National Heart, Lung, and Blood Institute. Initially, these devices were used exclusively for post-cardiotomy shock. In 1978, a left ventricular assist device (LVAD) was first used as a bridge to cardiac transplantation and in 2002, the U.S. Food and Drug Administration (FDA) approved the use of an LVAD for chronic, destination mechanical circulatory support in advanced HF.[91,92] As experience has grown, it has also been recognized that in select patients, implantation of an LVAD can promote recovery of myocardial function. Newer devices are smaller, more efficient, durable, and easier to implant surgically, and in some cases, percutaneously. With this evolution in technology, the promise of circulatory support as a viable option for many, if not all, patients with end-stage HF looks bright.

Candidate Selection

Failure of optimal medical therapy is the primary indication for circulatory assist device support. In acute HF, circulatory assist is needed in patients with postcardiotomy shock who are unable to be successfully weaned from cardiopulmonary bypass. It may also be necessary in the setting of persistent cardiogenic shock complicating an acute myocardial infarction or fulminant myocarditis. In chronic HF patients, circulatory assist is needed for patients who are failing medical therapy. These are generally stage D patients with end-stage

Table 18–5 Guidelines for Candidate Selection for Circulatory Cardiac Assist Support

A.	**Hemodynamic Criteria (on optimal medical therapy including balloon counterpulsation)**
	Cardiac index <2 L/min/m^2
	Systolic blood pressure <80 mm Hg
	Pulmonary capillary wedge pressure >20 mm Hg
B.	**Clinical Criteria (on optimal medical therapy for at least 60 days)**
	Marked functional limitation (NYHA class IV)
	LV ejection fraction <25%
	Inotrope dependence
	Peak $\dot{V}O_2$ < 12 mL/min/kg
	Inability to tolerate ACEI and β-blockers due to hypotension or renal failure
	Severe right ventricular dysfunction (for LVAD support only)
C.	**Assessment of Comorbidities**
	Diabetes
	Peripheral vascular disease
	Cerebrovascular disease
	Life-limiting systemic illness
D.	**Risk Factors for Suboptimal Outcome**
	Mechanical ventilation
	Postcardiotomy shock
	Reoperation
	Right atrial pressure >16 mm Hg (for LVAD support only)
	Prothrombin time >16 sec
	White blood cell count >15,000/mm^3
	Urine output <30 mL/hr
	Temperature >101.5° F
E.	**Technical Considerations**
	Body surface area <1.5 m^2
	Significant valvular pathology
	Right-to-left shunt
	Prosthetic valves
	Left ventricular thrombus
F.	**Atrial and Ventricular Arrhythmias**
G.	**Psychosocial Considerations**
	Current alcohol or drug dependence
	Significant mental illness
	Inadequate or absence of social support

ACEI, angiotensin-converting enzyme inhibitor; LVAD, left ventricular assist device; NYHA, New York Heart Association; $\dot{V}O_2$, oxygen consumption.

HF who may be on the cardiac transplant waiting list or who are candidates for destination therapy. There are no universal criteria for candidate selection, which is a complex process requiring clinical judgment and many considerations.[93] According to the ACC/AHA HF guidelines, permanent mechanical circulatory support is a class IIA recommendation for stage D patients.[94] The generally accepted criteria that are helpful in candidate selection are shown in Table 18–5.

Hemodynamic and Clinical Considerations

Criteria that define persistent hemodynamic and clinical compromise on optimal medical therapy include inotrope-dependence or intra-aortic balloon pump counterpulsation, factors that portend suboptimal short- and long-term outcomes after device implantation, and technical and psychosocial considerations. The benefit of intra-aortic balloon counterpulsation is short-lived and clinically insignificant in patients with nonischemic HF. The risk of infection and vascular compromise also precludes the use of balloon counterpulsation for more than 7 to 10 days.[95] Given the long waiting list times, balloon counterpulsation is generally not feasible as a bridge strategy and, in fact, in some centers circulatory support devices are implanted without a trial of balloon pump support. These criteria should be present after at least 60 days of optimal medical therapy as defined by the ACC/AHA guidelines.

Right ventricular function should be evaluated particularly thoroughly because it is the most important determinant of perioperative outcome after LVAD implantation. Patients who develop right ventricular failure have a higher early mortality rate, greater length of stay in intensive care, higher risks of reoperation for bleeding and renal failure, and lower survival to transplantation.[96] Unfortunately, there is no consensus on how best to assess right ventricular function in severe HF. Because routine echocardiographic assessment of the right ventricle is subjective and prone to error, more sophisticated analysis of contractile reserve using right ventricular pressure-area relations may be needed to accurately quantify right ventricular function.[97] In practice, however, right ventricular function is frequently assessed by collectively weighing the clinical, hemodynamic, and echocardiographic data. If severe right ventricular failure is present, then biventricular support or total heart replacement should be considered. Patient characteristics that predict the development of severe right ventricular failure after LVAD insertion include female gender, nonischemic etiology, elevated intraoperative central venous pressure, and low pulmonary artery pressure and right ventricular stroke work index.[98]

Secondary pulmonary hypertension is frequently present in patients with severe HF.[99] Although significant pulmonary hypertension by itself is not a contraindication to device implantation, its presence should be taken into consideration. It is important to remember that the absence or presence of only mild pulmonary hypertension does not always mean a lower risk for right HF because pulmonary pressures may be lower owing to significant right ventricular dysfunction and the inability of the right ventricle to generate an adequate output. On the one hand, mild pulmonary hypertension in the setting of a low cardiac output may actually become worse after device implantation when cardiac output is restored to normal. On the other hand, patients with significant pulmonary hypertension, who have preserved right ventricular function, may, in fact, lower their pulmonary pressures and resistance appreciably after device support. This strategy has been used successfully to help reverse significant pulmonary hypertension in transplant candidates.[100]

Assessment of Comorbidities

If present, comorbidities require as careful an evaluation as is done when considering candidates for cardiac transplantation. These comorbidities include diabetes, peripheral arterial and cerebrovascular diseases, and systemic illnesses.[101,102] Diabetic patients have to be screened for end-organ dysfunc-

tion. After device support, clinical outcomes in selected diabetics are similar to those in nondiabetic patients. Significant peripheral arterial disease and abdominal aortic aneurysm are relative contraindications. Because of the risk of thromboembolism after device implantation, patients should be screened for cerebrovascular disease. Mental status should be assessed in all potential candidates, as neurologic impairment is frequently encountered in patients who are in cardiogenic shock. It is important to determine if the neurologic dysfunction is reversible after restoration of cerebral blood flow with device support. Persistent neurologic dysfunction after device support precludes adequate physical rehabilitation that leads to poor long-term outcomes. Eligible candidates must not have a systemic illness, such as an active malignancy, that will limit life expectancy to 2 years or less.

Predicting Outcomes

The best outcomes are achieved in patients who undergo implantation of a circulatory assist device under elective conditions. Emergency device implantation is associated with a higher risk of death. Risk factors associated with poor outcome include significant right ventricular failure, mechanical ventilation, reoperation, laboratory parameters indicating end-organ dysfunction, and active infection. Previous sternotomy may be associated with increased postoperative bleeding. Reoperation to replace a temporary device such as an extracorporeal membrane oxygenator with a long-term circulatory assist device is also a risk factor.

The degree and number of organs affected by HF should be evaluated. Imaging studies are frequently needed if the laboratory parameters are abnormal. Many patients have mild-to-moderate renal impairment that requires temporary ultrafiltration or dialysis following device implantation. Hepatic dysfunction frequently resolves after device support, but it is critical that the coagulation profile be normalized before surgery. Liver dysfunction may be a risk factor for vasoplegia or excessive vasodilation on circulatory support. Device implantation should be postponed if active infection is present.[103]

In a retrospective analysis of 134 device implants in a single institution, preoperative creatinine clearance of less than 70 mL/minute, requirement for more than 1 inotrope, need for intra-aortic balloon for greater than 3 days, ischemic etiology for HF, diabetes, prior sternotomy, and absence of an internal cardioverter-defibrillator were independent univariate predictors of mortality after VAD placement. The presence of three or more of these risk factors was associated with a significantly shorter survival time on VAD support.[104] Other investigators have proposed a scoring system for risk assessment also based on the number of risk factors present at the time of device implantation. Although clinically useful, such a scoring system has not been prospectively validated.[105]

Technical Considerations

A small body surface area may preclude the use of currently approved intracorporeal devices. Extracorporeal support is needed for these patients. However, many of the newer devices are smaller and designed for use in pediatric and small adult patients. The presence of valvular disease must be taken into consideration.[106] Mitral stenosis, if severe, will require surgical correction at the time of device implantation to permit adequate filling of the device. Mitral regurgitation is encountered more frequently in advanced HF and is usually not a hemodynamic problem during device support. Typically, it improves acutely after device implantation due to decompression of the volume-overloaded left ventricle; this improvement is sustained during chronic device support. However, if myocardial recovery and device explantation are anticipated, mitral valve repair should be considered.

Aortic stenosis may not require surgical correction unless there is a possibility for recovery. Aortic regurgitation will limit the forward flow from the device and should be corrected by suturing the aortic leaflets together. If aortic valve replacement is considered, it is recommended that a bioprosthetic valve be used.

Tricuspid regurgitation, if severe, is frequently associated with significant right ventricular dysfunction. Lesser degrees of tricuspid regurgitation are often left alone because the experience with tricuspid valve repair during LVAD implantation is not very good. Immediately after device implantation, tricuspid regurgitation worsens because of volume loading of the right ventricle and shifting of the interventricular septum leftward. If the right ventricle can sustain this hemodynamic perturbation, over time there is no further worsening of tricuspid regurgitation. Experience with device implantation in patients with mechanical prostheses is limited.

An aortic prosthesis, in particular, can become thrombosed during device support related to blood stasis and inactivity of the prosthesis that remains in the closed position. Oversewing the valve and the use of a Dacron graft to occlude the outflow may reduce the risk of thromboembolism. A prosthesis in the mitral position is usually left alone with attention paid to chronic anticoagulation to reduce the risk of thromboembolism. Preoperatively, it is important to look for right-to-left shunting across a patent foramen ovale. Because of high left atrial pressures, these shunts are frequently not apparent until after device implantation and unloading of the left ventricle and atrium. Contrast echocardiography should be performed in the operating room after device implantation to look for a shunt that may require repair before separation from cardiopulmonary bypass.

Arrhythmias

Atrial arrhythmias may be important because they can impair adequate filling of the device. Ventricular arrhythmias are generally well tolerated in the absence of significant pulmonary hypertension that would prevent a passive Fontan-type circulation. In patients with recurrent ventricular arrhythmias and pulmonary hypertension, biventricular support is necessary. If there is a left ventricular apical mural thrombus, it should be removed at the time of device insertion, especially in a patient with acute myocardial infarction and cardiogenic shock.[107]

Psychosocial Factors

Psychosocial considerations are similar to those in transplant candidates. Current alcohol or drug dependence, lack of adequate social support, and significant mental illness that is difficult to treat are all risk factors for a poor long-term outcome.

Overview of Devices

It is extremely important to select the correct type of circulatory assist device in a given patient. A number of considerations influence this decision-making process, including emergency or elective implantation, body size, anticipated duration of support (bridge or destination), severity of right ventricular dysfunction, and the patient's eligibility for inclusion in a clinical trial. The menu for device selection continues to grow and, to date, there are no prospective data comparing one device with another.

The available devices can be categorized under extracorporeal devices, intracorporeal devices, axial flow pumps, centrifugal LVADs, total cardiac replacement devices, and percutaneous LVADs (Table 18–6; see also Appendix 3).

Extracorporeal Devices

These devices are outside the body and include the centrifugal pumps, the Abiomed BVS 5000, and the Thoratec (Pierce-Donachy) device.

Table 18–6 Overview of Circulatory Support Devices

Type	Name	Power Source	Type of Flow	FDA Approval	Anticoagulation	Patient Mobility	Duration of Use
Extracorporeal	ECMO	Electrical	Continuous	No	Yes	Limited	48-72 hrs
Extracorporeal	Abiomed BVS 5000	Pneumatic	Pulsatile	Yes (PCS)	Yes	Limited	7-10 days
Extracorporeal	Thoratec VAD	Pneumatic	Pulsatile	Yes (PCS, BTT)	Yes	Fair	Intermediate-term
Intracorporeal	Thoratec IVAD	Pneumatic	Pulsatile	Yes (BTT)	Yes	Good	Intermediate-term
Intracorporeal	HeartMate LVAS	Electrical (VE), Pneumatic (IP)	Pulsatile	Yes (BTT, DT)	No	Good	Long-term
Intracorporeal	Novacor LVAS	Electrical	Pulsatile	Yes (BTT)	Yes	Good	Long-term
Intracorporeal	LionHeart LVD 2000	Electrical	Pulsatile	No (DT*)	Yes	Good	Long-term
Axial Flow	HeartMate II	Electrical	Continuous	No (BTT*, DT*)	Yes	Good	Long-term
Axial Flow	Micromed DeBakey VAD	Electrical	Continuous	No (BTT*, DT*)	Yes	Good	Long-term
Axial Flow	Jarvik 2000	Electrical	Continuous	No (BTT*)	Yes	Good	Intermediate-term
Axial Flow	Incor LVAD	Electrical	Continuous	No (PCS*,BTT*)	Yes	Good	Short-term
Centrifugal	HeartMate III, Cor Aide, VentrAssist, Kriton, HeartQuest, DuraHeart	Electrical	Continuous	No	No	Good	Short-term
Total Cardiac Replacement	CardioWest TAH-t	Pneumatic	Pulsatile	Yes (BTT)	Yes	Fair	Intermediate-term
Total Cardiac Replacement	Abiocor	Electrical	Pulsatile	No (DT*)	Yes	Fair	Long-term
Percutaneous VAD	Tandem Heart PTVA	Electrical	Continuous	Yes (PCS)	Yes	Limited	7 days
Percutaneous VAD	Impella RS	Electrical	Continuous	No (PCS*)	Yes	Limited	7 days
Percutaneous VAD	Cancion CRS	Electrical	Continuous	No (HF exacerbation*)	Yes	Limited	7 days

See text for device abbreviation.
*Clinical trials underway.
BTT, bridge-to-transplantation; DT, destination therapy; PCS, postcardiotomy support.

Centrifugal Pumps

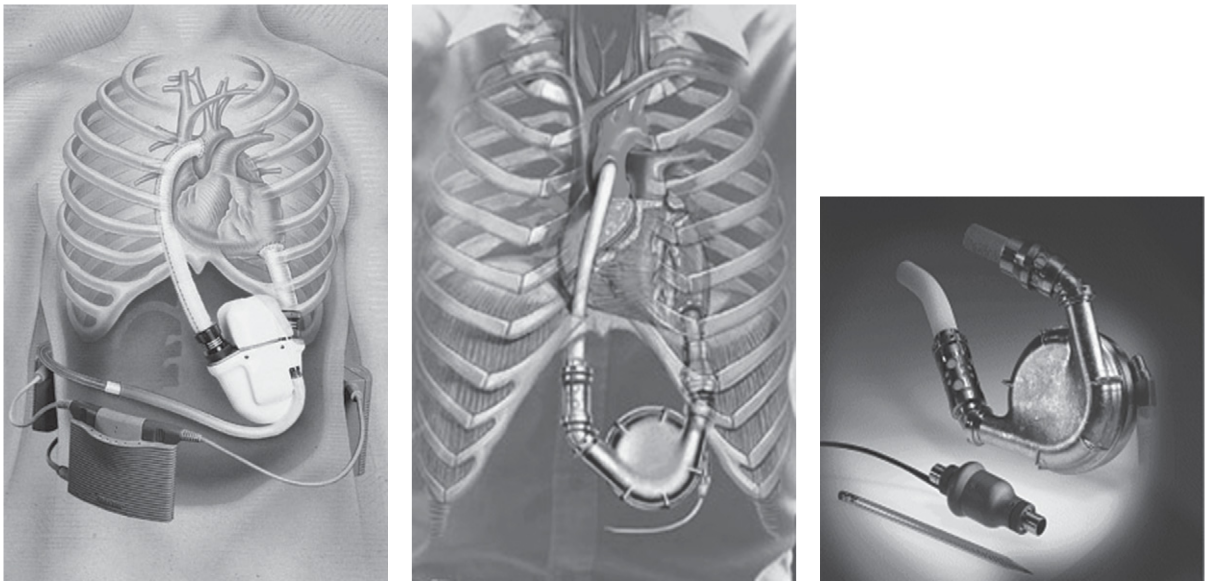
These are the devices used for cardiopulmonary bypass during cardiac surgery. They have an electrical power source and can be used to support right, left, or both ventricles. They use magnetic impeller cones with flow regulation by the rotation method and provide continuous flow. They cause less hemolysis than roller head pumps. Their implantation requires arterial, atrial, or ventricular cannulation. They are not FDA approved for circulatory support. Disadvantages of these pumps include the risk of coagulopathy, need for intravenous anticoagulation, only short duration of support (48 to 72 hours), the necessity for patients to remain in the intensive care unit, difficulty in closing the chest, and the need for bedside perfusion teams to run the system. A hollow fiber membrane oxygenator may be included in the system for extracorporeal membrane oxygenation (ECMO). In these patients, continuous monitoring of hematocrit and oxygen concentration in the pre- and postoxygenator circuits is needed. The use of ECMO for cardiopulmonary assist in adults has been disappointing. However, in patients with perioperative allograft failure following cardiac transplantation, an 84% weaning rate and a 52% survival rate were reported.[108-110]

Abiomed BVS 5000

This device is FDA approved for use in postcardiotomy shock. It is a pneumatic, pulsatile device that can be used to support the left, right, or both ventricles. The pump has two chambers, two polyurethane valves, and can achieve flows of up to 6 L/minute. It uses the left ventricle, left atrium, or right atrium for inflow cannulation. For left ventricular support, the outflow cannulation is into the ascending aorta, whereas it is into the pulmonary artery for right ventricular support. This device is self-regulating, fills via gravity, permits closure of the chest, and does not require a bedside perfusion team. Disadvantages of this device include the need for chronic anticoagulation with increased risk of bleeding, use for short to intermediate duration (7 to 10 days), and restricted patient mobility owing to the size of the console. Nevertheless, this is a device that can be used in community hospitals to stabilize patients before transfer to a specialized institution to await myocardial recovery or bridge to another longer-term device. Data from a worldwide registry indicate that this device has been used to support over 6000 patients (63% for postcardiotomy shock) with patient survival to explantation or transplantation approaching 50%.[111] A newer generation device (Abiomed AB 5000) that uses a smaller console is now available and this permits increased mobility and rehabilitation for supported patients.

Thoratec VAD

This ventricular assist device is a pulsatile, pneumatic, thromboresistant polyurethane-lined, pusher plate pump that can be used for right, left, or biventricular support (Fig. 18–4). The driver is connected via a pneumatic hose that delivers alternating pressure or vacuum inside the pump housing. With pressure, the blood sac collapses, resulting in ejection, whereas application of vacuum creates a pressure gradient that assists filling from the left ventricle. The dual drive console has two independent and identical drive modules for left and right ventricular support. It is FDA approved for both postcardiotomy shock and for use as a bridge to transplantation. Its placement is achieved via a median sternotomy on cardiopulmonary bypass.[112] For left-sided support, the inflow cannula is typically placed in the left ventricular apex and tunneled subcostally to the external pump. The outflow cannula is also subcostally tunneled and anastomosed to the ascending aorta. The left atrium can also be used for inflow cannulation, but this generally results in suboptimal flows. For right-sided support, the right atrium is used for inflow cannulation and the pulmonary artery for anastomosis of the outflow cannula. Unidirectional flow is maintained by Bjork-Shiley tilting disc prosthetic valves in the blood pump. The pump delivers a



A B C

Figure 18–4 Ventricular assist devices that are presently approved by the Food and Drug Administration in the United States. **A,** Novacor LVAS (electrical power, maximum flow 10 L/min). **B,** HeartMate XVE LVAD (electrical power, maximum flow 10 L/min). **C,** Thoratec VAD (pneumatic power, maximum flow 7.2 L/min). The Novacor LVAS and the Heartmate XVE are intracorporeal, whereas the Thoratec VAD is extracorporeal and can be used to assist both the right and the left ventricles.

maximum stroke volume of 65 mL, can achieve flows up to 7 L/minute, and can be operated in a fixed asynchronous mode or volume (full to empty) or synchronous (with R wave) mode.[113] This device is durable, versatile, and can be used in small adults and children. A compact and portable driver (TLC-II) is now available and when patients are ready to ambulate, they can be switched from the console driver to the TLC-II and discharged from the hospital.[114] According to the Thoratec VAD worldwide voluntary registry, more than 2800 patients have received these devices as of November 2004 with the longest duration of implantation being 566 days. Chronic anticoagulation is required with this device.

Table 18–7 Troubleshooting of the HeartMate LVAD in the Automode

Decreased LVAD rate	Increased LVAD rate
Filling slower = ↓ preload • Hypovolemia • Tamponade • RV dysfunction • Inflow cannula kink • LV function recovery	Filling faster = ↑ preload • Hypervolemia • Aortic insufficiency • Inflow valve regurgitation

Intracorporeal Devices

These implantable pulsatile devices include the Thoratec implantable ventricular assist device (IVAD), Thoratec HeartMate left ventricular assist system (LVAS), and the Novacor LVAS. All of these devices are implanted through a median sternotomy during cardiopulmonary bypass. The device is placed in a preperitoneal, subrectus pocket. Blood from the heart is channeled into the assist device through a tunneled inflow conduit that is attached to the apex of the left ventricle. The device, in turn, propels the blood in a pulsatile fashion through an outflow conduit that is tunneled and attached to the ascending aorta. Valves located in the inflow and outflow conduits ensure blood flow in only one direction. Precise placement of the inflow and outflow conduits and the routes by which they are tunneled are critical to prevent blood flow obstruction and erosive injury to the heart or the aorta. Inadequate de-airing of the LVAD may cause neurologic sequelae. A tunneled percutaneous driveline connects the device to its portable external driver. Design improvements to enhance patient comfort and mobility have resulted in smaller, lighter weight drivers with extended power packs for up to 6 hours. All of these devices enable patients to achieve full ambulation, resume all activities with the exception of swimming, and be discharged from the hospital.

Thoratec IVAD

The IVAD can be used as a bridge to transplantation or as a bridge to recovery in postcardiotomy shock patients.[115] It is the only FDA-approved implantable device that can be used for left, right, or biventricular support. The pump is made of a durable titanium alloy and has a smooth external profile. It accommodates a wide range of patient sizes and is connected to the portable TLC-II driver with a tunneled percutaneous driveline. The use of this device requires systemic anticoagulation. In the initial experience with this device, 68% of patients were successfully bridged to transplantation or recovery. The mean duration of IVAD support per patient was 82 days, with the longest duration of 298 days, without any unexpected adverse events or device failures.

Thoratec HeartMate LVAS

There are two approved versions of this device for left ventricular support only; the *Vented Electric (VE)* LVAD, which is powered by wearable batteries and the *Implantable Pneumatic (IP)* LVAD, which is powered by an external drive console.[116,117] Both are FDA-approved devices for use as a bridge to transplantation, and the VE LVAD is also approved for use as destination therapy (see Fig. 18–4). In both versions the pusher plate technology with a polyurethane diaphragm is used to propel blood in a pulsatile fashion. The inside of the device is coated with a textured blood contacting surface (composed of sintered titanium microspheres) that promotes adherence of blood elements leading to the development of a pseudointima that mimics the intimal lining of native blood vessels.[118] The inflow and outflow valves are both porcine xenografts. This unique design significantly reduces the risk of thromboembolism and avoids the need for systemic anticoagulation. This device can generate a stroke volume of 85 mL, with a maximum output of 10 L/minute. It can operate either in a fixed mode at a preset rate or an auto mode in which the device responds to changing physiologic flow demands of the patient (Table 18–7). If the activity level increases, requiring more blood flow, the increased flow through the heart triggers a similar increase in flow of the LVAD. Likewise, when flow demands decrease, flow through the device decreases as well. The device permits a fail-safe mechanism whereby in the event of pneumatic or electrical motor failure, it can be operated via a hand pump. As of November 2004, the HeartMate LVAS worldwide voluntary registry reported 1323 pneumatic and 2867 electrical LVAS implants. The average duration of the pneumatic implant was 97 days and the electrical implant 152 days; the maximum duration of pneumatic LVAD support was 805 days and the electrical LVAD support 1854 days.[119]

The Thoratec HeartMate XVE is an enhanced version of the VE LVAD that is now commercially available. The enhancements incorporated in this device include increased flexibility in the percutaneous lead, enhanced controller software to reduce wear of the valves and bearings, and a newly designed inflow valve that has greater durability.[120] Despite the design upgrade, durability remains an issue with this device, particularly when it is used for destination therapy. Device failure, which occurs at a rate of 15%, frequently involves inflow valvular regurgitation with recurrence of HF requiring elective replacement of the pump. Electrical power failure of the VE LVAD can sometimes be managed with the use of a pneumatic console, but may require emergency VAD replacement.

Novacor LVAS

This is an implantable, electrical, dual pusher plate, polyurethane-lined blood pump (see Fig. 18–4). It has two porcine-valved conduits. This device is known for its reliability and durability and was the first device used to bridge a patient to transplantation. It generates a stroke volume of 70 mL and can produce flows up to 10 L/minute. It is used only for left-sided support and is FDA approved as a bridge to transplantation.[121,122] Systemic anticoagulation is required,

and the thromboembolic risk with this device is high. Design changes (e.g., use of ePTFE inflow conduits) have however decreased this risk.[123] According to the Novacor LVAS worldwide registry, over 1100 implants have been performed with cumulative support of greater than 300 patient years, with only 0.7% requiring replacement. In the Novacor bridge to transplantation multicenter U.S. trial that enrolled 191 patients (156 device, 35 control), the mean duration of support was 80 days and the rate of survival to transplantation was 78%.[124]

Arrow LionHeart LVD 2000

This device is the first fully implantable LVAD for destination therapy. It is a pulsatile, volume displacement pump that uses energy from an external battery pack that is transmitted across the skin to power an implanted battery. Because there is no percutaneous driveline, infection rates on this device are much lower than other devices, and the patient can enjoy limited periods of untethered movements and activities. Initial experience in six patients at a single center in Europe demonstrated a 50% survival rate at 18 months with no device failures or device-related infections.[125] A U.S. feasibility trial is ongoing.

Axial Flow Pumps

The axial flow pumps are a new generation of nonpulsatile devices that are small, silent, easy to implant, and have simple mechanics with only one moving part and no valves (Fig. 18–5). Their small size and mechanical simplicity offer considerable advantage and benefits over the previously described first-generation pumps. An abdominal pocket is not needed and implantation can be done without cardioplegic arrest. A flexible inflow cannula is connected to the apex of the left ventricle and the outflow cannula is connected to the ascending or descending aorta. These pumps can generate flows between 8 and 10 L/minute. They are used to support only the left ventricle and their use requires systemic anticoagulation. Device failure is rare and causes severe aortic regurgitation requiring emergency replacement of the pump. There is, however, a risk of hemolysis. Although short-term nonpulsatile flow does not appear to affect organ function, the physiologic relevance of permanent loss of pulsatility is unknown at this time. The currently available axial flow pumps include the HeartMate II LVAS, Micromed DeBakey VAD, Jarvik 2000 Flowmaker, and the Incor (Berlin Heart) LVAD.[126-129] All of these devices are investigational in the United States.

HeartMate II LVAS

This device incorporates a textured surface similar to the HeartMate XVE that is resistant to thrombosis. A small percutaneous driveline connects to an external controller and power pack that share the same hardware platform and system components as the HeartMate XVE LVAS. A phase I pilot trial with this device was completed and a phase II pivotal trial is underway. This trial has two arms: one that will enroll 133 patients who are candidates for cardiac transplantation prospectively in a nonrandomized fashion, and another that will prospectively randomize 200 patients who are ineligible for transplantation in a 2:1 fashion to either the HeartMate II LVAS or the HeartMate XVE LVAS for destination therapy.

Micromed DeBakey VAD

This device is the size of a "C" battery, measures 1″ × 3″, and weighs only 4 ounces. More than 300 patients have been supported with this device worldwide and it is approved for use as a bridge to transplantation in Europe. In the United States, clinical trials are underway to evaluate its efficacy and safety both for bridge to transplantation and destination therapy in end-stage HF.

Jarvik 2000 Flowmaker

This device has been used to treat more than 100 patients in Europe and the United States. In 79% of patients, the device was used as a bridge to transplantation. In this group, survival to transplantation was 70%. The longest a patient has been supported with this device is 5 years. This device is approved in Europe for both bridge to transplantation and destination therapy. In the United States, clinical trials are currently underway to evaluate the safety and efficacy of this device as a bridge to transplantation.

Incor LVAD

In its first clinical experience, the Incor LVAD was evaluated in 15 patients with cardiogenic shock. One patient was weaned, five patients were bridged to transplantation, and three were on support at the time of the report. The overall survival rate was 60%.

A B C

Figure 18–5 The axial flow pumps that are presently under investigation. **A,** HeartMate II LVAS. **B,** Micromed DeBakey VAD. **C,** Jarvik 2000 Flowmaker.

Centrifugal LVADs

The centrifugal LVADs are investigational, third-generation pumps in which the rotating assembly is magnetically suspended and noncontacting and, therefore, has no mechanical wear with chronic use.[130] Potentially, these pumps can provide significantly longer periods of circulatory support than the previously described devices. No systemic anticoagulation is needed. The centrifugal LVADs currently in clinical development are the HeartMate III LVAS, CorAide pump, VentrAssist pump, Kriton pump, HeartQuest pump, and Dura Heart LVAS.

Total Cardiac Replacement

These devices are totally implantable and they orthotopically replace both ventricles and all four valves. They are particularly suited for those patients who have biventricular failure, cardiac arrhythmias, fixed pulmonary hypertension, interventricular shunts, intracardiac thrombus, and mechanical prosthesis and who are not candidates for a left ventricular assist device. Two devices that are currently available for total cardiac replacement include the CardioWest Temporary Total Artificial Heart (TAH-t), and the Abiocor replacement heart system. The American BioMed Baylor-TAH, the Cleveland Clinic Foundation Nimbus-TAH, and the MagScrew TAH are currently under investigation.

CardioWest TAH-t

This is the only FDA-approved total cardiac replacement device in the United States.[131] It evolved from the Jarvik-7 total artificial heart and is a pneumatic, pulsatile, biventricular blood pump lined with polyurethane. In the United States, the device is powered by a large console that prevents discharge from the hospital; whereas in Europe, portable drivers are used permitting discharge from the hospital. This device requires systemic anticoagulation. In a nonrandomized, prospective study, the safety and efficacy of this device were evaluated in transplant-eligible patients who had irreversible biventricular failure. Eighty-one patients were implanted with the device and the survival to transplantation was 79%. In 35 historical control patients who did not receive the device, the survival to transplantation was significantly lower at 46%. The one-year survival rate in patients receiving the device was 70%, which was significantly better than 31% in the control group.

Abiocor Replacement Heart System

This is an investigational, electrical, pulsatile device made of titanium and polyurethane plastic with fully implantable components.[132] These components include the pump, energy transfer device, internal battery, and controller. The pump is implanted in the thorax. The internal battery is continually recharged from an external battery pack using the energy transfer device called TET (transcutaneous energy transmission). The TET system consists of internal and external coils that transmit power across the skin without piercing the surface. Chronic anticoagulation is required with this device. The safety and efficacy of the Abiocor replacement heart system are currently being evaluated in an FDA-approved clinical trial. In the initial reported experience, seven patients received the Abiocor device, and there were five deaths during follow-up. The actual survival at 30 days was 71%, and at 60 days it was 43%. Predicted survival on medical therapy alone at 30 days was 13%. Total days on support with the Abiocor are 759 days. This multicenter trial is ongoing.

Percutaneous VADs

These magnetically levitated centrifugal pumps are electrically powered and can frequently be implanted without sternotomy or cardiopulmonary bypass. They are, therefore, ideally suited for circulatory support during high risk, percutaneous coronary intervention, for patients with cardiogenic or postcardiotomy shock, or for patients with acute HF exacerbation that is refractory to pharmacologic therapy. The percutaneous VADs currently available include the Tandem Heart PTVA system, Impella Recover system, and Cancion CRS therapy.[133-135] The Tandem Heart PTVA is approved by the FDA, whereas the other two devices are investigational. These pumps can generate up to 4 to 6 L of flow for 5 to 7 days and their use requires systemic anticoagulation.

Tandem Heart PTVA

This system pulls oxygenated blood from the left atrium and returns it to the systemic arterial circulation. An inflow cannula is advanced retrograde through the femoral vein transseptally into the left atrium. The outflow cannula is inserted into the femoral artery.

Impella Recover System

This is a microaxial pump that can be used to support either the right or the left ventricle. For left ventricular support, the device is inserted retrograde via the femoral artery and advanced into the left ventricle through the aortic valve. For right ventricular support, a sternotomy is needed and the pump with the suction chamber is implanted into the right atrium with the outflow cannula in the pulmonary artery.

Cancion CRS Therapy

This therapy increases blood flow in the descending aorta inducing vasodilation and increased renal blood flow. It uses two arterial cannulas: an inflow cannula in the femoral artery and an outflow cannula in the descending aorta. In a pilot study with 24 patients, continuous aortic flow augmentation with the Cancion CRS therapy achieved both hemodynamic improvement (increase in cardiac index and lowering of systemic vascular resistance) and ventricular unloading (decrease in pulmonary capillary wedge pressure) that persisted for 24 hours after device therapy was discontinued. In animal models of HF, this therapy has been shown to reverse neurohormonal and vascular signaling. The clinical and biologic effects of this therapy in end-stage HF that is inadequately responsive to medical therapy are currently being evaluated in a randomized, controlled trial.

Destination Therapy

Because short-term use of circulatory assist devices improves symptoms, normalizes hemodynamics, and restores quality of life with a relatively low incidence of adverse events, the suitability of these devices as permanent long-term therapy in end-stage HF patients was evaluated in the *Randomized*

*E*valuation of *M*echanical *A*ssistance for the *T*reatment of *C*ongestive *H*eart failure (REMATCH) trial.[92] This prospective trial randomized 129 patients who were ineligible for transplantation 1:1 to either optimal medical therapy or a HeartMate XVE LVAD. The inclusion criteria ensured that this was a truly end-stage study population (71% of patients were on inotropic support at the time of randomization) with a very high anticipated mortality. Kaplan-Meier survival curves demonstrated a 48% reduction (P = 0.003) in all-cause mortality in the LVAD group compared with the medical therapy group. The survival rate at 1 year was 52% in the device group and 25% in the medical therapy group (P = 0.002), and the survival rate at 2 years was 23% and 8%, respectively (P = 0.09). The patients enrolled in REMATCH were considerably sicker than the patients enrolled in pharmacologic studies in advanced HF (Table 18–8). The quality-of-life measures were significantly improved in the device group at 1 year. Terminal HF was the most frequent (93%) cause of death in the medical therapy group, whereas infection (41%) and device failure (17%) were the most common reasons for death in the LVAD group. The number of days in and out of the hospital was longer in the LVAD-supported patients.

Based on the results from the REMATCH trial, the FDA approved the HeartMate LVAD for destination therapy in end-stage HF patients who are transplant ineligible. Subsequent modification in device design and adoption of strict infection control guidelines have significantly improved outcomes on LVAD destination therapy. Data from the four highest volume destination therapy centers in the United States now demonstrate a 1-year survival rate of 61% in LVAD-supported patients, which is a 40% improvement over the REMATCH data (Fig. 18–6). Fatal device failure rate has been reduced to 15% and the fatal infection rate to 8%.[136] Because malnutrition is an important predisposing risk factor for infection, it is important to optimize nutrition before LVAD surgery. It is anticipated that continued enhancement in device design and greater experience with patient selection and management will lead to further improvements in outcomes for LVAD patients in the future, approaching those seen with cardiac transplantation. The eligibility criteria established by the U.S. Food and Drug Administration (FDA) for destination therapy were adopted by the Center for Medicare and Medicaid Services (CMS) in October, 2003 (Table 18–9).

The results of the *I*nvestigation of *N*on-*Tr*ansplant *E*ligible *P*atients who are *I*notrope-*D*ependent (INTrEPID) trial, which was a nonrandomized, multicenter study of the Novacor LVAS in 55 New York Heart Association (NYHA) functional class IV patients, who were not eligible for transplantation, were reported. As with the REMATCH trial, the 6-month and 1-year survival rates in the 37 patients who received the LVAS were significantly better than the control group of 18 patients (46% versus 22% at 6 months and 27% versus 11% at 1 year, respectively). Both infection and cerebrovascular events accounted for 16% of deaths in the LVAS group. The quality-of-life scores were better in the LVAS group and 85% of the device-supported patients improved to NYHA class I to II symptoms.

There are three destination therapy trials currently in progress, all of which are prospectively comparing another circulatory assist device with the HeartMate XVE LVAD in patients who are not transplant candidates. The *R*andomized *E*valuation of the Novacor *LVAS In A Non-Transplant* population (RELIANT) trial is randomizing patients in a 2:1 ratio to the Novacor LVAS and the HeartMate XVE, whereas the *D*estination *E*valuation *L*ong-*T*erm *A*ssist (DELTA) trial is using a 2:1 ratio to the Micromed DeBakey VAD and the HeartMate XVE. A third trial is randomizing patients in a 2:1 fashion to the HeartMate II LVAS and HeartMate XVE. With the successful completion of these trials, several devices will likely become available for destination therapy and physicians will have the opportunity to match the appropriate device to

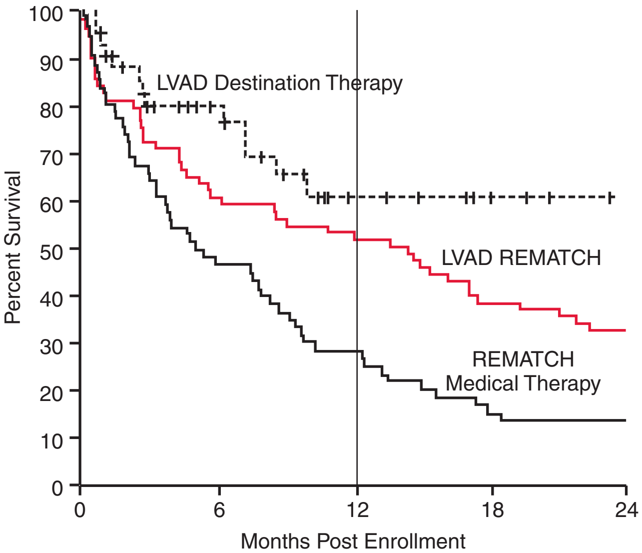


Figure 18–6 Long-term survival with HeartMate XVE LVAD destination therapy: Comparison with REMATCH results. (Redrawn from Long JW, Kfoury AG, Slaughter MS, et al: Long-term destination therapy with the HeartMate XVE left ventricular assist device: Improved outcomes since REMATCH study. Congest Heart Fail 2005;11:133-8, with permission.)

Table 18–8 Patient Characteristics in Class III-IV Heart Failure Trials

	REMATCH	FIRST	PROMISE	COPERNICUS	RALES	CONSENSUS
LVEF (%)	17	19	20	21	25	—
NYHA Class	IV	IV	III-IV	IIIB-IV	III-IV	IV
SBP (mm Hg)	103	105	115	123	122	119
Sodium (mEq/L)	135	137	139	137	—	138
Creatinine (mg/dL)	1.8	—	1.5	1.5	1.2	1.4
1-year mortality (%)	75	49	40	18.5	24	45

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

Table 18–9 FDA and CMS Criteria for Destination Therapy

Not a candidate for cardiac transplantation
NYHA class IV end-stage LV failure
Life expectancy <2 years
Failure of symptoms to respond despite optimal medical management for ≥60 of past 90 days
LVEF < 25%
Peak $\dot{V}O_2$ < 12 mL/min/kg or inotrope dependence
BSA ≥ 1.5 m^2

BSA, body surface area; CMS, Center for Medicare and Medicaid Services; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; $\dot{V}O_2$, oxygen consumption.

any given patient based on objective criteria so that long-term outcome on destination therapy is optimal.

Management of Patients on VAD

Although patient selection is a critical determinant for a good outcome after LVAD support, proper management of patients on support is also important for a successful outcome. A team approach to care is needed, and the key members of the team frequently include a nurse coordinator, engineer, cardiologist, and surgeon. Education of the patient and caregiver is vital to successful VAD management, as it is with any complex therapy. It is also important to ensure that paramedics and health care workers in fire departments and emergency rooms close to the patient's home are educated so that they can participate in the care of emergency issues.

Acute Management

Following LVAD insertion, the acute management issues include bleeding, right ventricular failure, and atrial and ventricular arrhythmias. However, selecting the proper patient and the proper device may minimize the risk of bleeding and right ventricular failure.

Bleeding

If there is significant mediastinal bleeding, reoperation is necessary to avoid tamponade. The risk of bleeding is greater with earlier sternotomy, hepatic dysfunction, and implantation of pulsatile intra- and extracorporeal devices and total cardiac replacement devices rather than the axial flow pumps. Bleeding that requires multiple transfusions of blood products can overburden the right ventricle causing right ventricular failure. Multiple transfusions can also cause noncardiogenic pulmonary edema leading to respiratory failure.

Right Ventricular Failure

Right ventricular dysfunction can be treated with inhaled nitric oxide to reduce pulmonary vascular resistance or intravenous milrinone to augment contractility in addition to causing pulmonary vasodilation. Among patients who stabilize, intravenous therapy may be needed for several days. Persistent, severe right ventricular failure with LVAD under filling and low flows requires insertion of a right ventricular assist device (RVAD). In general, when RVAD is needed following LVAD placement the outcome is poorer when compared with a priori biventricular support. Therefore, recognizing who is at risk for needing an RVAD preoperatively is important so that biventricular support or total cardiac replacement can be considered in these high-risk patients. Emergency device implantation, elevated serum creatinine and prothrombin time, mechanical ventilation, and low pulmonary artery pressure or cardiac index, or right ventricular stroke work index are all risk factors that predict the need for biventricular support.[137]

Arrhythmias

Both atrial fibrillation and serious ventricular arrhythmias can develop postoperatively and limit LVAD filling. Prompt restoration of normal rhythm either with pharmacologic or electrical cardioversion is critical. Serious ventricular arrhythmias are more frequent in patients with ischemic heart disease and if present early (within the first week) portend a poor outcome. Patients who do not respond to drug therapy frequently require RVAD insertion.

Chronic Management

According to the ISHLT Mechanical Circulatory Support Database (MCSD) analysis of 655 device patients (78% bridge to transplant) from 66 centers worldwide, the 6-month survival rate was 67% and the 1-year survival was 50%.[138] The major causes of death were multiorgan failure (35%), bleeding (15%), cardiovascular (12%), cerebrovascular accident (10%), and infection (8%). Right ventricular failure with need for RVAD, older age, female gender, ventilator support at the time of device implant, diabetes, and elevated creatinine and white cell count were risk factors for death after device implant. Freedom from device malfunction was 84% at 6 months and 66% at 1 year.

The chronic management issues of device support include anticoagulation, risk of thromboembolic complications, local (driveline) or systemic infection, systemic hypertension, arrhythmias, device failure, and HF. In addition, management of any coexistent noncardiac conditions such as diabetes, thyroid disease, and anemia is important—just as in other HF patients. Chronic care of the patient needs to be coordinated between the VAD team and the local physicians.

Anticoagulation

Thromboembolic transient ischemic attacks and strokes remain dreaded complications of device therapy and careful monitoring of anticoagulation is imperative. Over-anticoagulation with systemic, gastrointestinal, or intracranial bleeding is also of concern, and the INR needs to be monitored at least monthly. All VADs except for the HeartMate LVAS and the investigational centrifugal pumps require chronic warfarin therapy with a targeted INR of 3.0 to 3.5. The textured surface of the HeartMate LVAS permits the development of a pseudointima that reduces the risk of thromboembolism and the need for chronic anticoagulation. However, in the REMATCH trial, neurologic events were common with 44% of patients in the device group sustaining at least one event and 16% having either an ischemic or hemorrhagic stroke.[139] Certain devices such as the Novacor LVAS have been associated with a higher risk (23%) of fatal thromboembolic and cerebrovascular events than others such as the HeartMate XVE, although with recent design improvements (use of ePTFE inflow conduits) the risk of such events on Novacor

LVAS support has decreased significantly. The risk of a neurologic thromboembolic event decreases with increasing duration of support. All anticoagulation protocols combine warfarin and aspirin, and some also include dipyridamole or clopidogrel, or both.

Infection

Continued surveillance against driveline, pocket, and systemic infections is critical to optimizing outcome on device support. Older patients and patients with diabetes or renal dysfunction may be particularly prone to infectious complications. Obese individuals receiving intracorporeal devices may be predisposed to pocket infections. Antibiotic prophylaxis before dental, urologic, gastrointestinal, or gynecologic procedures is recommended.

Systemic Hypertension

Systemic hypertension has been noted in patients on chronic support with pulsatile LVADs. The incidence may be as high as 69%, and this can be detected as early as 7 days after LVAD insertion. There are no predisposing risk factors and this tends to occur both in chronic dilated and ischemic cardiomyopathy as well as acute cardiomyopathy and myocardial infarction patients. The cause is unclear and potential mechanisms include elevated vasomotor tone, malfunction of the cardiorenal axis, and neurohormonal activation. The incidence of hypertension correlates with device flow and its presence is associated with a higher incidence of neurologic events. The majority of patients respond to a single antihypertensive agent such as an ACE inhibitor, although resistant hypertension requiring multiple drugs has been noted.

Arrhythmias

Chronic atrial fibrillation, if present, should be treated by usual methods aimed at rhythm and rate control. Persistent rapid atrial fibrillation can impair filling and reduce LVAD flow. Sustained ventricular tachycardia or ventricular fibrillation during chronic LVAD support has been noted in 22% of patients. The arrhythmias are more prevalent in patients with ischemic HF and can be treated with either antiarrhythmic drug therapy or radiofrequency ablation. If an internal cardioverter-defibrillator (ICD) is present before implantation, it should remain activated. Patients receiving biventricular support may have their ICD removed after device implantation. There have been no reported incidents of LVAD-ICD interaction.

Device Failure

In the REMATCH trial, the probability of device failure at 2 years was 35%, and 10 patients (out of 67) required device replacement.[140] In a recent report, the rate of device failure was 15% with the use of the Thoratec HeartMate XVE for destination therapy. No device failures were reported in the INTrEPID trial with the Novacor LVAS. Inflow valve regurgitation and inflow cannula obstruction in the LVAD can result in recurrence of HF. This can be diagnosed by cardiac catheterization and requires device replacement.

Heart Failure

Patients on LVAD support require drug therapy for chronic HF. Treatment with ACE inhibitors and β-blockers should be continued because many patients have chronic right ventricular dysfunction and continued use of such therapy may aid in myocardial recovery. HF therapy is not needed during biventricular or TAH support. Cardiac resynchronization therapy (CRT), if present before implantation, can be turned off following LVAD insertion.

Myocardial Recovery on Circulatory Support

The progression of ventricular dysfunction in HF patients is characterized by cellular, molecular, structural, and functional changes that involve all components of the myocardium leading to alterations in myocardial architecture and geometry that is referred to as cardiac remodeling.[141,142] This progressive remodeling in turn leads to the hemodynamic alterations that are characteristic of HF. The exact mechanisms for these changes are unclear but mechanical stretch of myocytes, activation of neurohormonal, cytokine, and inflammatory pathways, and increased expression of matrix metalloproteinases may all be involved. There is considerable evidence to suggest that chronic unloading with a ventricular assist device not only restores normal hemodynamics and function, but also reverses, at least partially, the histologic, biologic, cellular, and molecular changes associated with HF (Table 18–10). Despite this, the number of patients who exhibit clinical recovery that results in successful VAD explantation remains variable and rather small—possibly because partial or complete normalization of HF-associated transcriptional responses occurs only in a small number of VAD-supported patients.[143,144]

In one series of 111 implants only five patients (4.5%) were explanted for myocardial recovery.[145] In another series of 131 VAD insertions in dilated cardiomyopathy patients, 32 patients (24.4%) were weaned successfully. The recovered patients had a 5-year survival rate of 78%. Left ventricular end-diastolic dimension greater than 55 mm and/or ejection fraction less than 45% before LVAD removal, as well as history of HF for 5 years or more before LVAD implantation, were risk factors for recurrence of HF after device explantation. Almost all patients demonstrating recovery had positive anti-β_1-adrenoceptor autoantibody titers.[146,147] In a third series of 154 patients who underwent device implants, there were 10 patients who exhibited recovery that allowed explantation. Patients demonstrating recovery underwent VAD implantation either for postcardiotomy shock or for severe HF from dilated cardiomyopathy. The incidence of recovery allowing explantation was 11% in the dilated cardiomyopathy group. No patient with chronic ischemic cardiomyopathy demonstrated recovery. The 1-year transplant-free survival in the explanted group was 80%.[148] Patients demonstrating recovery were younger women with a shorter duration of HF before VAD implantation. Based on these observations, it appears that sustained myocardial recovery after VAD explantation can be expected only in young patients with recent-onset dilated cardiomyopathy. Evidence for recovery peaks at around 60 days of support.

There is no consensus as to how the potential for myocardial recovery should be clinically evaluated in a VAD-supported patient. Echocardiographic assessment on and off pump is a good screening test in clinically stable, ambulatory patients. Patients whose clinical profile favors recovery on VAD support should have a resting echocardiogram on and

Table 18–10 Effects of Chronic Unloading with VAD

A. Hemodynamic and Functional Effects
Increased cardiac index
Decreased pulmonary capillary wedge pressure
Decreased pulmonary vascular resistance
Normalization of end-diastolic pressure-volume relation
Decreased cardiothoracic ratio
Decreased left ventricular dimensions
Decreased left ventricular mass
Decreased left atrial size
B. Histologic Effects
Decreased wavy band fibers
Decreased contraction band necrosis
Decreased myocytolysis
Decreased collagen deposition
Increased fibrosis
C. Biologic Effects
Decreased plasma renin activity
Decreased angiotensin II
Decreased epinephrine
Decreased norepinephrine
Decreased arginine vasopressin
Decreased interleukin-6
D. Cellular Effects
Decreased myocyte size and volume
Regression of myocyte hypertrophy
Improved contractility
Increased inotropic response to β-adrenergic stimulation
E. Molecular Effects
Upregulation of *Fas*
Downregulation of TNFα
Normalization of ANP, BNP immunoreactivity
Downregulation of MMPs
Improved cytosolic Ca^{2+} transients
Upregulation of SERCA
Changes in cytoskeletal proteins (sarcomeric, nonsarcomeric, and membrane-associated)
Improved myocardial mitochondrial function

ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; MMP, matrix metalloproteinase; SERCA, sarcoplasmic reticulum calcium ATPase; TNF, tumor necrosis factor.

off pump monthly after device implantation. If the left ventricular end-diastolic dimension is less than 55 mm, and ejection fraction is greater than 45%, hemodynamic testing and maximal exercise with gas exchange analysis should be done at minimal support, to further establish functional recovery. The resting hemodynamics must be near normal and the maximal exercise oxygen consumption achieved should be similar to that seen in an NYHA class II patient (greater than or equal to 14 mL/kg/minute). In addition, there should be reductions in both QRS and corrected QT intervals from the pre-implantation ECG and a reduction in serum BNP levels. On-line quantitative echocardiography is another useful tool to ascertain recovery because it measures load-independent variables of cardiac function.[149] Increased stroke area, greater than 40% increase in fractional area change, or preload adjusted maximal power greater than 4.0 mW/cm^4 at low device flow (e.g., 1 to 2 L/minute) is often associated with successful device explantation. This technique is not widely available and can be used alone or in combination with maximal exercise testing and gas exchange analysis.

Combining pharmacologic therapy specifically aimed at reversing remodeling may increase the likelihood of myocardial recovery on VAD support.[150] Clenbuterol is a β_2-adrenergic receptor agonist that induces physiologic cardiac hypertrophy and reverses many of the adverse cellular and molecular changes in pressure-overloaded animal models of hypertrophy and HF. In a pilot series of 15 patients with dilated cardiomyopathy, clenbuterol therapy starting with 40 mcg twice a day with up titration to 700 mcg three times a day, in addition to ACE inhibitors, β-blockers, and aldosterone antagonists enabled successful device explantation in 12 patients (80%). Clenbuterol induced an increase in the myocardial expression of insulin-like growth factor (IGF)-1, which is an atrophy and apoptosis-limiting protein that also promotes regeneration. IGF-I expression returned to normal 1 year after LVAD explantation in this study.[151] These results are encouraging and a multicenter clinical trial is presently exploring the benefit of this promising strategy.

Future Directions

In the continuum of HF care, the role of circulatory assist devices continues to be redefined. From its initial application for short-term circulatory support as a last resort in cardiogenic shock, considerable progress over the years has resulted in the current use of these devices for destination therapy in chronic HF. During this period of evolution, the devices have become smaller, increasingly durable, and reliable—which has, in turn, enhanced the confidence in this therapy among health care providers. Further, chronic ventricular unloading with circulatory assist devices appears to result in partial or complete myocardial structural, functional, and molecular recovery. This recovery may be augmented by pharmacologic induction of cellular hypertrophy or myogenesis using cell therapy. In the future, application of circulatory support devices may not be only for temporary support of the failing circulation in end-stage HF patients awaiting transplantation, but also for induction of myocardial recovery of structure and function in patients with lesser degrees of HF.

With the anticipated increase in demand for devices in HF, special attention needs to be paid to the cost of circulatory assist device therapy. The cost burden of HF care in the United States is not only enormous and amounts to $24 billion annually, which is approximately 2% of the national health care budget, but also continues to escalate. In the REMATCH trial, the average cost of care among patients receiving the LVAD and surviving to discharge was $160,000, whereas it was $315,000 among the nonsurvivors.[152,153] The economic impact of an unfavorable outcome with an LVAD is, therefore, substantial. The median payment from CMS for an LVAD implant today is $128,000. In contrast, the cost of care for advanced HF patients on continuous inotropic therapy is between $40,000 and $130,000 annually, with no hope for increased survival. The challenge to clinicians in the future is not only to recognize the correct HF patients for circulatory assist device therapy, but also to appropriately time the implantation to maximize cost-effective prolongation of survival.

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SECTION 4

Arrhythmias/Conduction Disturbances

Chapter 19

Clinical Pharmacology of Antiarrhythmic Drugs

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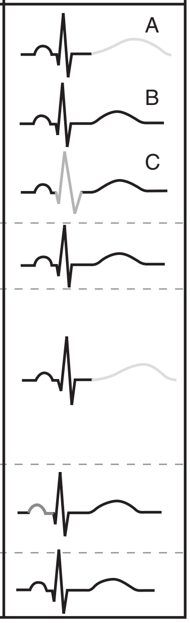
CHAPTER CONTENTS

Antiarrhythmic drugs have been developed with the expectation that they would extend and improve life for many patients with cardiovascular disease and for those with a history of life-threatening arrhythmias. Their usefulness, however, has been limited by ineffectiveness and/or toxicity. In mortality trials, benefit has not been clearly demonstrated, and worsened mortality rates have been observed with several drugs. Care must be taken, therefore, in deciding the mode of treatment, or in fact whether or not to treat at all. The use of antiarrhythmic drugs has been dramatically altered by the findings of the Cardiac Arrhythmia Suppression Trial (CAST).[1] This landmark study was designed to test the hypothesis that suppression of asymptomatic ventricular arrhythmias in patients with recent myocardial infarction would reduce mortality rates from cardiac arrest and/or arrhythmic sudden death. In 1989, the CAST was interrupted by the Data Safety and Monitoring Committee, and encainide and flecainide arms were removed because they had been found to increase mortality rates by two- to threefold. With the loss of confidence in sodium-channel blocking drugs, attention turned to drugs such as amiodarone that prolong cardiac refractorinesss. Although these drugs are effective in controlling symptomatic arrhythmias, their effects on mortality rates have been unclear but are probably neutral.[2,3] The other development in the treatment of serious ventricular arrhythmias has been the automated internal cardioverter-defibrillator. The trial that compared antiarrhythmic drugs with such devices, Antiarrhythmics Versus Implantable Defibrillators (AVID), found the device to have a greater improvement in mortality rates.[4,5] However, many patients with the devices continue to require treatment with antiarrhythmic drugs, and interactions (both desirable and undesirable) between the drugs and devices have been documented. Generally, drugs that block sodium channels can increase pacing and defibrillation thresholds, and drugs that prolong refractoriness, potassium-channel blocking drugs, lower the defibrillation threshold.[6,7]

Antiarrhythmic drugs are often classified according to their electrophysiologic effects.[8] The scheme most often used was originally proposed by Vaughan Williams as a classification of drug actions that should be antiarrhythmic.[8] Because of the limitations of the Vaughan Williams classification, another approach has been proposed,[9] termed the *Sicilian gambit*. This classification system is based on the differential effects of antiarrhythmic drugs on (1) channels, (2) receptors, and (3) transmembrane pumps. The grouping is based primarily on the predominant action of drugs but also considers the other ancillary actions that may be clinically relevant. Figure 19–1 is a combination of the Sicilian gambit and the Vaughan Williams classification, and it includes a comparison of their clinical effects and ECG changes. For example, quinidine, a class IA drug, is a sodium channel antagonist with abilities to block potassium channels and antagonize acetylcholine and catecholamines at cholinergic and α-adrenergic receptors, respectively. When this information is combined with an understanding of the electrophysiologic role of these actions, one can predict the effects that are likely to occur in vivo. In this case, one would expect conduction slowing, increased

ANTIARRHYTHMIC DRUG ACTIONS

Vaughn-Williams Class	DRUG	CHANNELS			RECEPTORS				Clinical Effects				ECG Changes
		Na	Ca	K	α	β	ACh	Ado	Pro-Arrhy	LV FX	Heart Rate	Extra Cardiac	
I A	Quinidine	M		H	L		M		H			M	A
I A	Procainamide	M		M					M			H	
I A	Disopyramide (Norpace)	M		M			M		L	↓↓		M	
I B	Lidocaine (Xylocaine)	L							L			M	B
I B	Mexiletine (Mexitil)	L							L			M	
I C	Propafenone (Rythmol)	H				M			M	↓↓	↓	L	C
I C	Flecainide (Tambocor)	H							H	↓↓		L	
II	β-Adrenergic antagonists					H			L	↓	↓↓	L	
III	Bretylium (Bretylol)			H	▲	▲			L		↓	L	
III	Sotalol (Betapace)			H		H			H	↓	↓	L	
III	Amiodarone (Cordarone)	L	L	H	M	M	M		L		↓	H	
III	Ibutilide (Corvert)	△		H					H			L	
III	Dofetilide (Tikosyn)			H					H			L	
IV	Verapamil (Calan, Isoptin)		H						L	↓↓	↓	L	
IV	Diltiazem (Cardizem)		M						L	↓	↓	L	
Misc	Adenosine (Adenocard)							△	L		↓	L	



Antagonist relative potency	
L = Low M = Moderate H = High	△ = Agonist ▲ = Agonist / Antagonist

Figure 19–1 (*See also Color Plate 19–1).* This is a modification of the Sicilian Gambit drug classification system and includes designation by the Vaughan Williams system. The sodium channel blockers are subdivided into the A, B, and C subgroups based on their relative potency. The targets of antiarrhythmic drugs are listed across the top in columns. These targets are the ion channels—sodium, calcium, and potassium—and the receptors—α-adrenergic, β-adrenergic, cholinergic (ACh), and adenosinergic (Ado). The next columns show a comparison of the clinical actions of the drugs, including proarrhythmic potential (Proarrhy), effect on left ventricular function (LV FX), effects on heart rate (Heart Rate), and potential for extra cardiac side effects (Extra Cardiac). The electrocardiographic tracings indicate the changes (*in color*) that are caused by usual dosages of the drug: PR interval (*blue*), QRS interval (*red*), and QT interval (*green*). The drugs are listed in rows with their brand names shown in parentheses. The symbols in the table indicate the relative potency of the drugs as agonists or antagonists. The *solid triangle* indicates the biphasic effects of bretylium to initially release norepinephrine and act as an agonist and subsequently to block further release and to act as an antagonist of adrenergic tone. The *number of arrows* and their directions indicate the magnitude and direction, respectively, of the effect of the drugs on heart rate and left ventricular function (i.e., inotropy).

action potential duration (APD) (and refractoriness), and vasodilation to result from these three actions of quinidine.

This chapter reviews the clinical pharmacology of the currently available antiarrhythmic drugs, excluding digoxin, β-receptor antagonists, and calcium channel blockers, which are addressed in other chapters. The drugs reappear in the same order as listed in Figure 19–1, a modified version of the Sicilian gambit classification. An understanding of clinical pharmacologic principles is essential when prescribing drugs that have narrow therapeutic indices, such as antiarrhythmic drugs (see Appendix 1 for a discussion of clinical pharmacology and tabular summaries of the pharmacokinetics, dosing, and plasma concentrations of the antiarrhythmic agents reviewed in this chapter). Individualization of dosage and plasma level monitoring have become standard with these drugs, but it is important to emphasize that there are many factors, such as chiral clearance and active metabolites, that create variability in the relationship between plasma concentrations and drug action.[10] This variability results in the need for clinicians to monitor clinical response whenever possible and not to place undue reliance on reaching the "therapeutic range" because it may not be therapeutic.

QUINIDINE

The effective dosage of quinidine varies among individuals because of several factors. Although quinidine sulfate is usually administered every 6 hours, there are wide interindividual differences in its elimination half-life, which ranges from 3 to 19 hours.[11] Plasma protein binding also varies widely, ranging from 50% to 95%.[11] Oral bioavailability is approxi-

mately 70%, and clearance after oral administration ranges from 200 to 400 mL/minute. Quinidine is inactivated or eliminated by both hepatic metabolism (50% to 90%) and renal elimination (10% to 30%). Several potentially active metabolites are formed in amounts that vary among individuals,[12] but for most, their clinical role has not been determined. One of the metabolites of quinidine, 3-hydroxyquinidine, has been shown to possess antiarrhythmic activity when administered to humans.[12] Experimental data indicate some contribution by metabolites of quinidine to its antiarrhythmic action.[13-15]

Marked prolongation of the QT interval has been seen in some patients receiving low or usual dosages of quinidine, and the risk of torsades de pointes is markedly increased. This arrhythmia may be responsible for most cases of quinidine syncope, which occurs in as many as 5% to 10% of patients within the first days of quinidine treatment, and for quinidine-induced sudden death.[16] Torsades de pointes usually occurs in patients (females more than males) with low serum concentrations of quinidine, hypokalemia, poor ventricular function, and bradycardia.[16,17] In a study by Drici and colleagues, dihydrotestosterone reduced the sensitivity to the effects of quinidine on the QT interval in animals.[18] This study[18] and subsequent studies,[19,20] in which women were shown to be more sensitive to the effects of quinidine on the QT interval, provide evidence that sex hormones have direct effects on cardiac tissue that may be responsible for the difference in baseline QT interval[21] and the incidence of torsades de pointes in men and women.[17,22]

For patients who develop torsades de pointes, treatment with pacing or isoproterenol is very effective. Magnesium sulfate injection (2 g IV bolus with 2 to 4 g repeated once, if necessary) is often recommended as initial therapy for torsades de pointes, although controlled trials are not available. These measures should also include correction of hypokalemia (to levels >4.0 mEq/L). Clinically, it is essential to distinguish torsades de pointes from polymorphic ventricular tachycardia occurring in the setting of a normal QT interval, because the latter should be treated with local anesthetic antiarrhythmic drugs and may be worsened by the above treatment for torsades de pointes.

Because quinidine acts via α-adrenergic blockade to produce vasodilatation,[23] hypotension may occur, especially in patients concomitantly receiving nitrates or other vasodilators. Other adverse effects include a high incidence of diarrhea and vomiting, tinnitus at high plasma levels, rare thrombocytopenia,[24] and, in unusual cases, conduction block in patients with existing conduction system disease.[25] In patients treated with quinidine for atrial flutter without prior atrioventricular (AV) nodal blockade by digitalis, there have been reports of sudden increases in AV conduction and rapid ventricular rates.[23] This results from a slight reduction of the flutter rate and enhanced AV nodal conduction due to the anticholinergic effects of quinidine. This permits 1:1 conduction through the AV node, often at 200 to 250 beats per minute. This may be of particular concern for patients receiving other drugs that increase conduction time through the AV node, such as β-adrenergic agonists.

Individualization of Dosage

Quinidine therapy (as the sulfate) is usually initiated with an oral dosage of 200 mg every 6 hours, and the dosage is titrated every 3 or more days. Elderly patients often require lower dosages of quinidine because of both reduced clearance and volume of distribution.

Quinidine is available commercially in at least three different forms: quinidine sulfate, gluconate, and polygalacturonate. Because the quinidine content varies among these at 83%, 62%, and 60%, respectively, the need for dosage adjustment should be considered if one form is substituted for another. The usually effective dosage of quinidine sulfate ranges from 800 to 2400 mg/day, with the maximum recommended single dose being 600 mg. Because the half-life varies from 3 to 19 hours, one should wait 4 days between dosage increases to prevent unexpected drug accumulation. The range of therapeutic plasma concentrations measured using assays that differentiate quinidine from its metabolites is 0.7 to 5.5 mcg/mL.[26,27] Rapid escalation in quinidine dosage has been used to convert atrial fibrillation, but this therapy is no longer recommended because of unacceptable toxicity.

Intravenous therapy with quinidine is usually avoided if alternatives are feasible. Vasodilation and hypotension result from quinidine-induced α-adrenergic blockade. If quinidine is administered intravenously (as quinidine gluconate), the patient's blood pressure should be monitored and the infusion rate should be no greater than 16 mg/minute. The infusion should be discontinued if hypotension is observed or the QRS is prolonged by more than 30%.

Modification of Dosage in Disease States

No adjustment in initial dosage is usually needed for patients with renal or hepatic disease,[28,29] although due to decreased protein binding in patients with hepatic failure, lower-than-usual total plasma concentration can produce toxicity.[30] Slower dose titration is advisable to permit attainment of steady state and complete accumulation of active metabolites; however, because the usual range of effective dosages is wide, dosage for these patients is not markedly different. Patients with rapid quinidine elimination may require higher dosages (up to 600 mg every 6 hours). This is often due to induction of hepatic metabolism caused by other drugs.

Patients with congenital long-QT syndrome, hypokalemia, or a history of torsades de pointes[31] should not be administered quinidine because of their increased risk for this form of proarrhythmic event. For patients with congestive heart failure, problems associated with use of quinidine are proarrhythmia and digitalis (either digitoxin or digoxin) toxicity. Prudent use of quinidine in individuals taking digitalis requires that (1) titration begin at a reduced dosage; (2) dosage of any cardiac glycoside being administered concomitantly be reduced; and (3) plasma electrolyte levels, especially potassium, be maintained above 4 mEq/L.

Although quinidine does possess some direct negative inotropic effects, these are usually counteracted by its vasodilatory effect; therefore, oral quinidine is well tolerated hemodynamically when administered at dosages producing usual plasma concentrations, even in patients with reduced ventricular function.[32] In a study of more than 650 patients, of whom 35% had congestive heart failure, quinidine therapy resulted in no induction or worsening of congestive heart failure.[25] On the other hand, a significant problem for patients with congestive heart failure receiving quinidine therapy is proarrhythmia, with quinidine-induced torsades de pointes

being potentiated in the setting of bradycardia and low serum levels of magnesium or potassium.[33,34]

Drug Interactions

Quinidine metabolism is inhibited by cimetidine[35] and induced by phenytoin, phenobarbital,[36] and rifampicin,[24] with the latter agents leading to reduced, often subtherapeutic, quinidine concentrations. Clinical digoxin toxicity has been described in 20% to 40% of patients receiving quinidine and digoxin concurrently.[35] The magnitude of this interaction is dependent on quinidine dosage, and in some patients it may not appear until the dosage is increased to higher levels.[37,38] The rise in digoxin levels appears with the first dose of quinidine; therefore, it is suggested that digoxin dosage be halved when quinidine therapy is initiated. A similar interaction has been reported for quinidine and digitoxin.

Quinidine is a potent inhibitor of the hepatic cytochrome P450 (CYP) specific for debrisoquine metabolism (CYP2D6),[39,40] although it is not metabolized by this specific CYP isozyme.[41,42] Thus, it may interfere with the biotransformation and actions of pharmacologic agents that are dependent on this cytochrome for their metabolism, which include propafenone, mexiletine, flecainide, metoprolol, timolol, sparteine, and bufuralol.[43] Quinidine worsens neuromuscular blockade in patients with myasthenia gravis[44] and may prolong the effects of succinylcholine.[45]

PROCAINAMIDE

Procainamide is rapidly absorbed and 100% orally bioavailable. About 15% of procainamide is bound to serum proteins. The short half-life of elimination of procainamide of 2 to 4 hours in patients with normal renal function necessitates dosing every 3 to 6 hours. Dosing every 6, 8, or 12 hours is possible with sustained-release preparations, and the frequency depends on the formulation. The varied formulations and their very different dosing requirements often create confusion and can lead to dangerous mistakes in dosing.

Slightly more than one half of the general population are phenotypic rapid acetylators of procainamide and quickly convert it to *N*-acetylprocainamide (NAPA), a metabolite with pure class III antiarrhythmic action.[46] As would be expected, however, the response to one agent does not predict response to the other. When each is administered as the sole agent, the usually effective plasma concentration is 4 to 8 mcg/mL for procainamide and 7 to 15 mcg/mL for NAPA.[46] During oral procainamide therapy, both agents are present in variable amounts, and there is no way to determine readily the contribution of NAPA to arrhythmia suppression under these conditions. Consequently, the usefulness of measuring plasma levels of procainamide during chronic therapy is limited because of this variable hepatic conversion to NAPA. Monitoring plasma concentrations for determination of compliance or prevention of toxicity is feasible and recommended (see later).

Individualization of Dosage

Procainamide is available for either intravenous or oral use. With normal renal and cardiac function, the initial recommended oral maintenance dose is 50 mg/kg/day. Frequent administration is required for oral procainamide, which is inconvenient and makes compliance difficult. Sustained-release forms of procainamide are available, which permit dosing every 6, 8, or 12 hours, depending on the formulation. During chronic therapy, levels of NAPA may accumulate to effective or toxic levels in some individuals, resulting in achievement of maximum pharmacologic effect long after the time procainamide has reached steady state.[46,47] Therefore, the elimination half-life of 2 to 4 hours for procainamide may be misleading as a predictor of time to the occurrence of stable pharmacologic action. Thus, dosage should be initiated at conservative levels, and the patient should be monitored carefully until both procainamide and its metabolite have reached steady state. Patients with ventricular tachycardia may need higher dosages[46] for the prevention of arrhythmia induction by programmed stimulation,[48] although such dosages often lead to adverse effects. Because the electrophysiologic effects of procainamide and NAPA are quite different, monitoring of patients receiving procainamide should at some point include measurement of plasma concentrations of both agents to determine their relative concentrations. Patients who are rapid acetylators or who have impaired renal function usually have plasma concentrations of NAPA higher than procainamide at steady state. These individuals should be monitored for excessive accumulation of NAPA during dose titration to maintain plasma levels of NAPA below 20 mcg/mL. The practice of using the sum of the plasma concentration of procainamide and NAPA is not recommended.

When administered intravenously, procainamide can be administered as a constant 25-minute loading infusion of 275 mcg/min/kg of body weight or in a series of doses (100 mg delivered over 3 minutes) given every 5 minutes, up to a total dose of 1 g.[49,50] If the loading infusion is well tolerated with no hypotension and less than 25% QRS or QT widening, a maintenance intravenous infusion of 20 to 60 mcg/kg/min can then be administered. Larger and more rapid loading infusions of 1 g over 15 to 20 minutes have been administered in the electrophysiology laboratory to prevent induction of ventricular tachycardia by programmed ventricular stimulation. A second loading infusion of 0.5 to 1 g has been administered in some instances where an initial loading infusion was well tolerated but ineffective. These large dosages are accompanied by a higher incidence of hypotension and conduction disturbance and often result in attainment of an unacceptably high plasma concentration.

Modification of Dosage in Disease States

With renal dysfunction or a low cardiac output, both procainamide and NAPA in usual doses may accumulate to potentially toxic levels and the dose should be reduced.[51] Increased plasma levels of procainamide and/or NAPA may occur with congestive heart failure because of decreased urinary excretion and hydrolysis of procainamide.[52] On the other hand, one study of procainamide pharmacokinetics following a single intravenous bolus revealed no difference in volume of distribution, clearance, elimination half-life, unbound drug fraction, and peak procainamide concentrations between patients with congestive heart failure and normal individuals.[53] Although intravenous procainamide does depress myocardial

contractility and lower blood pressure, worsening of heart failure is uncommon during oral therapy when the usual dosages and plasma concentrations are maintained.

Drug Interactions

Unlike quinidine, procainamide does not cause an increase in digoxin levels. There are few reports of interactions between procainamide and other drugs. Its clearance is reduced 30% to 50% by cimetidine, which blocks the renal tubular secretion of procainamide.[54,55] A similar competition has been found between procainamide and its predominant metabolite, NAPA.[56] Ranitidine affects procainamide pharmacokinetics by reducing both its renal clearance and its absorption, the former by 14% to 23% and the latter by 10% to 24%, depending on the dose.[57]

DISOPYRAMIDE

The oral bioavailability of disopyramide is 80% to 90%.[58] Its half-life of elimination, usually 6 to 8 hours, is lengthened to as much as 15 hours in cardiac patients.[59] About one half of the compound is eliminated by the kidneys unchanged, and the remainder as an active metabolite, resulting from hepatic *N*-dealkylation.[60] Protein binding of disopyramide is complex, with 20% to 50% of disopyramide being bound to plasma proteins. For most drugs, the percentage bound to plasma protein is a constant over the usual range of therapeutic concentrations. The saturation of disopyramide-binding sites on plasma proteins at usual doses means that there are disproportionate increases in levels of free drug in plasma compared with the magnitude of dosage increment.[61]

Individualization of Dosage

Loading doses are not recommended with disopyramide because of saturable protein binding. The usually effective dosage for disopyramide is 100 to 400 mg three to four times daily, to a maximal dose of 800 mg daily. Therapy should be titrated, beginning with low doses (100 mg three times daily) and allowing ample time (2 to 4 days) for achievement of steady-state equilibrium.

Although rapid fluctuations in plasma concentration are undesirable, they are difficult to avoid because of the saturable protein binding of disopyramide. The controlled-release form of disopyramide may be useful in reducing adverse effects by decreasing fluctuations in the concentration of free disopyramide in plasma.[62] Because of saturable protein binding,[63] the generally accepted therapeutic range for total disopyramide in plasma of 2 to 5 mcg/mL should not be strictly relied on. Although monitoring of the plasma concentrations of free disopyramide has been recommended,[64] the range of concentrations associated with arrhythmia suppression has not been clearly delineated and overlaps with that causing adverse effects.

Modification of Dosage in Disease States

Patient response to disopyramide should be monitored especially closely after acute myocardial infarction because both the absorption and elimination of disopyramide are decreased at this time.[65] In fact, in view of the negative inotropic actions and changes in levels of binding proteins in plasma after a myocardial infarction associated with disopyramide, other antiarrhythmic agents should be considered first. Disopyramide is contraindicated in patients with uncompensated heart failure because it can worsen failure.[66] The initial dosage of disopyramide should be reduced to 50 to 100 mg every 12 hours in patients with renal insufficiency[67] or decreased hepatic function.[68]

Drug Interactions

Disopyramide does not increase digoxin levels,[69] and the effects of warfarin are not potentiated by disopyramide.[70] Phenytoin, rifampicin, and phenobarbital induce hepatic metabolism (CYP3A4 mediated)[71] of disopyramide, thus increasing its elimination and potentially leading to loss of the antiarrhythmic effect.[72] Significant depression of myocardial contractility may result from the combined administration of disopyramide with β-adrenergic or calcium channel antagonists and should be avoided in patients with impairment of ventricular function.[73]

LIDOCAINE

Orally administered lidocaine is well absorbed, but it has poor oral bioavailability because it undergoes extensive first-pass hepatic metabolism. Lidocaine clearance is well approximated by measurement of the liver blood flow.[74,75] The two desethyl metabolites, which are excreted by the kidneys, have less antiarrhythmic potency than the parent drug and may contribute to the production of central nervous system side effects occurring with lidocaine.[76,77] After intravenous administration, the biphasic disposition of lidocaine is well represented by a two-compartment pharmacokinetic model.[78] Because antiarrhythmic activity is correlated with the concentration of lidocaine in the central compartment and because the half-life of distribution out of this compartment is rapid (8 minutes), regimens that include a series of multiple loading doses and a maintenance infusion should be used to achieve and maintain a therapeutic concentration in plasma and myocardial tissue (see later).

Regardless of the initial regimen used, during prolonged constant infusion, the lidocaine concentration eventually reaches steady state—dependent on drug infusion rate and the clearance of lidocaine. The time required to reach steady-state conditions is approximately 8 to 10 hours in normal individuals and up to 20 to 24 hours in some patients with heart failure and/or liver disease. This is longer than often anticipated because of the failure to recognize the relatively long elimination half-life (1.5 to 2 hours in normal subjects and longer in patients with heart failure or hepatic disease).

Individualization of Dosage

The primary use of lidocaine is for acute rapid suppression of highly symptomatic ventricular arrhythmias. Single intravenous boluses will achieve only transient therapeutic effects because the drug is rapidly distributed out of the plasma and myocardium; therefore, multiple loading doses should be used

to rapidly achieve more sustained therapeutic plasma levels of lidocaine. Based on pharmacokinetic models validated in clinical studies, several regimens have been designed to maintain a relatively constant therapeutic level. For a stable patient, a total loading dose of lidocaine should be approximately 3 to 4 mg/kg body weight administered over 20 to 30 minutes. After injection of an initial dose of 1 mg/kg over 2 minutes, a series of three loading ''boluses'' can be administered slowly (approximately 50 mg each over 2 minutes) at 8 to 10 minutes apart, while the patient is continuously observed for the development of side effects. Loading should be stopped should the transient, usually mild, central nervous system side effects persist or serious unwanted effects occur.

Another effective and well-tolerated loading regimen was suggested by Wyman and coworkers.[79] For a 75-kg person, an initial bolus of 75 mg is recommended, followed by 50 mg every 5 minutes repeated three times to a total dose of 225 mg. This regimen usually achieves and maintains plasma concentrations within usual therapeutic guidelines (1.5 to 5 mcg/mL). A priming dose of 75 mg followed by a loading infusion of 150 mg over 18 minutes has also been used successfully.[80] At the time of initiation of the loading regimen, a maintenance infusion, designed to replace ongoing losses due to drug elimination, should be started. This may be calculated as the product of the desired plasma concentration (about 3 mcg/mL) and the expected clearance. This calculation usually yields a dosage in the range of 20 to 60 mcg/kg/min.

Even in normal individuals, there is great variability in the peak plasma concentration and, consequently, in the calculated size of the central compartment for lidocaine. Therefore, during loading, the patient's electrocardiogram, blood pressure, and mental status should be monitored; the process should be stopped at the first sign of lidocaine excess. When symptomatic arrhythmias persist in the presence of documented adequate dosage, defined by side effects or plasma concentration in excess of 5 to 7 mcg/mL, another agent should be used.

If the maintenance infusion has reached steady state but the concentration is below the level needed to prevent recurrence and the arrhythmia reappears while side effects are absent, the appropriate actions are as follows:

1. Obtain a plasma sample for measurement of the lidocaine concentration for future reference.
2. Administer a small bolus of lidocaine (25 to 50 mg over 2 minutes).
3. Increase the maintenance infusion rate proportionally.

The plasma concentration can be used to estimate clearance for calculation of the final maintenance infusion (i.e., maintenance dosage equals clearance multiplied by the desired plasma concentration, and clearance equals infusion rate divided by the plasma concentration measured at steady state). Little therapeutic effect is evident at lidocaine plasma concentrations below 1.5 mcg/mL, whereas the risk of toxicity increases above 5 mcg/mL. In some patients, however, concentrations in the range of 5 to 9 mcg/mL may be required for arrhythmia suppression and can safely be achieved with cautious drug administration (e.g., monitoring for signs of neurologic toxicity from lidocaine).[81]

Once steady-state conditions have been achieved, simply terminating a lidocaine infusion will result in a gradual decline in plasma levels over the next 8 to 10 hours as elimination occurs. Not only is there no reason to taper lidocaine infusions, but also it may be dangerous if oral antiarrhythmic therapy is initiated too early because unpredictable additive effects may occur between lidocaine and newly started oral therapy. If a patient has reached steady-state equilibrium, it is possible to estimate when the plasma lidocaine concentration will fall below usually therapeutic levels. The plasma lidocaine concentration should be determined at the time the infusion is terminated, and the number of half-lives needed for that level to reach approximately 1.5 mcg/mL can be estimated. The half-life of lidocaine for an individual patient can be estimated from the following equation:

$$t_{1/2} = \frac{\text{plasma concentration} \times V_D \times 0.693}{\text{infusion rate}}$$

where V_D is the final volume of distribution. The measured plasma concentration and the infusion rate are known components of the equation. V_D is usually 1.1 L/kg but may be reduced by 50% or more in patients with heart failure.

Modification of Dosage in Disease States

Initial loading regimens require no adjustment in patients with renal or liver disease[78]; however, maintenance infusions must be decreased in liver disease and heart failure to compensate for decreased clearance. Because clearance alone is altered in liver disease with little change in the volume of distribution, the half-life of elimination is prolonged greatly (as much as 5 hours) and steady-state conditions may not be achieved until 20 to 25 hours after the institution of an intravenous infusion. Despite the fact that lidocaine metabolites are excreted by the kidneys, renal disease has not been reported to exert any significant effect on lidocaine dosing regimens. With mechanical ventilation, there is often a decrease in cardiac output and hepatic blood flow, and a decrease in lidocaine dosage may be required.[82] Patients with congestive heart failure achieve lidocaine levels that are almost double those in normal individuals who are administered the same dose.[78] Because the central volume of distribution is generally halved in heart failure, loading doses should be reduced by 50%. Because clearance is also approximately halved, maintenance doses should be reduced proportionately from an infusion rate of 30 mcg/kg/min used for usual patients to about one half that figure. The time required to achieve steady-state conditions after the institution of a maintenance infusion is still 8 to 10 hours in many patients with heart failure because of concomitant changes in V_D and clearance, resulting in a half-life similar to that seen in patients without heart failure.

General recommendations for initial lidocaine dosage selection should be adjusted for each patient based on clinical presentation, clinical response, and the results of plasma level monitoring. Some patients with congestive heart failure may experience toxicity when given an infusion as low as 0.5 mg/mL, so blood level monitoring is essential for proper dosage adjustment. In postmyocardial infarction patients receiving lidocaine infusions for longer than 24 hours, plasma lidocaine levels can increase and the elimination phase half-life can increase up to 50%.[83] This increase is due, in part, to

changes occurring in protein binding of lidocaine during the first few days of therapy. Assays for plasma lidocaine measure the sum of both protein-bound and free lidocaine as total lidocaine and, thus, do not give a true picture of the amount of free drug available. An increase in plasma lidocaine occurring at this time often reflects an elevation in plasma levels of alpha-1-acid glycoprotein (AAG), to which it binds,[84] and does not always indicate an increase in free, active drug. In this case, the lidocaine dosage should not be reduced to compensate for the higher total plasma concentration—as long as the patient displays no adverse effects. Subsequent decreases in AAG concentrations will result in an apparent decrease in plasma lidocaine, which may reflect a drop in only that fraction bound to AAG.

Drug Interactions

An additive or synergistic depression of myocardial function or conduction may occur when using lidocaine combined with other antiarrhythmic agents,[85] especially during conversion from lidocaine to another antiarrhythmic agent. A pharmacokinetic drug interaction between propranolol and lidocaine has been described experimentally and in humans in which β-adrenergic blockade caused decreases in cardiac output and liver blood flow with a resultant decrease in lidocaine clearance.[86] Cimetidine has been reported to decrease the volume of distribution of lidocaine, to decrease splanchnic (and hence liver) blood flow, and to inhibit the enzymes responsible for lidocaine metabolism. CYP1A2 and CYP3A4 are responsible for most of the hepatic metabolism of lidocaine.[87] This may raise lidocaine plasma concentrations and both loading and maintenance dosages may require downward adjustment by 25% in patients who are receiving cimetidine.[88]

MEXILETINE

The systemic bioavailability of mexiletine approximates 90%,[89] with a large volume of distribution (5.5 to 9.5 L/kg), reflecting extensive tissue uptake. About 1% of total body content of mexiletine is in the plasma compartment, with approximately 70% of this bound to serum proteins. Mexiletine has little first-pass metabolism but is eliminated primarily by hepatic metabolism, with only 10% to 15% being excreted unchanged in the urine. Its half-life of elimination is between 8 and 20 hours (9 and 12 hours for healthy subjects), with the time needed to reach steady state ranging from 1 to 3 days.[90] Mexiletine undergoes extensive hepatic metabolism by CYP2D6,[91-93] and, consequently, clearance is extremely variable (see later).[94]

Individualization of Dosage

Mexiletine therapy should be initiated with a low dosage, which is increased at 2- to 3-day intervals until efficacy or intolerable side effects such as tremor or other central nervous system symptoms develop. With normal renal function, the recommended initial oral mexiletine dosage is 200 mg every 8 hours. As with most drugs having extensive liver metabolism, clearance will be widely variable within the population. This is especially true for mexiletine because CYP2D6, responsible for its metabolism, is absent in 7% of the white population. Also, consideration of dosage adjustment to compensate for the action of agents (discussed later) that induce or inhibit hepatic mexiletine metabolism is required.

Modification of Dosage in Disease States

Patients with renal failure who also inherit a deficiency of hepatic CYP2D6 are likely to have extremely slow elimination for mexiletine,[95] and for this reason, all renal failure patients should be administered low initial doses. Elimination half-life and clearance may be prolonged by overt congestive heart failure[96] and hepatic failure,[97] and dosage reduction by 50% is required.

Drug Interactions

The hepatic metabolism of mexiletine can be increased by phenobarbital, phenytoin, or rifampicin, which reduce the half-life of mexiletine, possibly changing an effective dose to an ineffective one. [90,98,99] Conversely, if treatment with an inducing agent is stopped, an effective dose may become toxic.

In one study, mexiletine decreased the clearance and increased the plasma concentrations of theophylline.[100] Quinidine inhibits the CYP2D6 enzyme primarily responsible for metabolic clearance of mexiletine, and the plasma concentration of mexiletine may increase in those individuals who express the enzyme (93% of whites).

PROPAFENONE

Propafenone has a marked structural similarity to propranolol, and studies have shown that propafenone can accumulate during continued administration to levels capable of producing clinically significant β-adrenergic inhibition.[101] Propafenone, like mexiletine and flecainide, is eliminated by a metabolic pathway that has a polymorphic pattern of inheritance. Patients deficient in CYP2D6 activity have very slow elimination of propafenone and fail to form measurable quantities of the potentially active metabolite 5-hydroxypropafenone.[102,103] The accumulation of high concentrations of propafenone leads to significant β-receptor antagonism at both low and high dosages in poor metabolizers of propafenone but only at high dosages in extensive metabolizers.[104] Although metabolic phenotype does not seem to dramatically influence the antiarrhythmic response to propafenone in many patients,[102] it clearly influences the degree of β-blockade occurring during therapy.

Individualization of Dosage

Effective dosages range from 300 to 900 mg daily in two to four divided doses. To prevent unexpected accumulation of pharmacologic action, propafenone dosage should not be changed more frequently than every 3 days; there is slow elimination of the parent drug in poor metabolizers, and there is slow accumulation of the metabolites in extensive metabolizers. Patients with reduced ventricular function, especially those receiving propafenone, should be carefully monitored

for deterioration in ventricular function, which may result from β-adrenergic receptor antagonism and/or the direct negative inotropic effect.[105]

Modification of Dosage in Disease States

Reduced dosages are recommended for patients with hepatic dysfunction but dosage reductions are not required for patients with renal insufficiency.

Drug Interactions

It is very likely that there will be drug interactions between propafenone and other agents that use or inhibit cytochrome CYP2D6 for their metabolism. Such an interaction has been documented already between propafenone and metoprolol[106] and should be expected with timolol, many antidepressants, many neuroleptics, and perhaps other agents. Quinidine, which inhibits this cytochrome, inhibits the formation of 5-hydroxypropafenone in extensive metabolizers[107]; however, the clinical consequence of such inhibition is unknown and difficult to predict. Greater β-blockade occurs after combining quinidine with propafenone therapy because of the resulting higher propafenone concentrations.[108]

FLECAINIDE

The systemic bioavailability of oral flecainide is 90% to 95%,[109] and most of flecainide is metabolized in the liver to compounds that are not pharmacologically active at the concentrations usually found in plasma.[110] Flecainide, like many other antiarrhythmic agents, is metabolized by CYP2D6.[111] Because flecainide is also eliminated by the kidneys to a considerable extent, the enzyme deficiency has little effect on the pharmacokinetics of flecainide. If, however, patients without the enzyme develop renal insufficiency or if renal failure patients are administered a drug that blocks the metabolism of flecainide, extremely high plasma concentrations are likely to occur.[112] A potential advantage of flecainide is its very slow elimination, with a half-life ranging from 7 to 23 hours in normal individuals and tending to be even longer (14 to 26 hours) in patients with cardiac disease, even in the absence of heart failure.[109,113]

Individualization of Dosage

The usual dosage of flecainide for ventricular arrhythmias is 100 to 150 mg every 12 hours in patients without cardiac or renal failure. A total daily dosage of more than 400 mg may sometimes be used under close medical monitoring (see later). It is recommended that patients with supraventricular tachycardia receive 50 mg every 12 hours as a starting dose. The range of therapeutic plasma concentrations of flecainide is reported to be between 200 and 1000 ng/mL, although adverse effects may occur in some patients at concentrations within this range,[114,115] and many patients tolerate concentrations well above this range. To reduce the incidence of adverse effects, flecainide therapy should start with a low dosage that is maintained until steady state has been reached (at least 4 days) and altered relative to clinical response.

Modification of Dosage in Disease States

With cardiac failure, the usual initial dose is 50 to 100 mg every 12 hours. Because 7% of white patients with renal failure will not have the CYP2D6 enzyme and because flecainide is usually eliminated via both metabolism and renal excretion, all patients with renal failure should be administered very low dosages and titrated. Plasma concentration monitoring is essential in patients with renal disease or cardiac or hepatic dysfunction. Any significant reduction in ejection fraction should be expected to lengthen elimination half-life and, hence, the time needed to attain steady-state equilibrium, whereas reductions in clearance may occur in renal or hepatic dysfunction and lead to higher plasma concentrations at steady state.

Drug Interactions

Cimetidine reduces flecainide clearance and prolongs flecainide elimination half-life.[116] Studies in normal volunteers have demonstrated an increase in the plasma concentrations of digoxin and propranolol when flecainide is coadministered.[117,118] Not unexpectedly, propranolol and flecainide have been found to have additive negative inotropic effects. An interaction with amiodarone, resulting in elevation of the plasma flecainide concentration and necessitating reduction of the flecainide dosage, has been described.[119]

SOTALOL

Sotalol blocks cardiac potassium channels (class III antiarrhythmic activity) and also possesses β-adrenergic antagonist activity. Oral bioavailability of sotalol is greater than 90%, and peak concentrations are seen 2.5 to 4 hours after a dose. It is not bound to plasma proteins and is eliminated by the kidneys unchanged, with an elimination half-life of approximately 12 hours. Because of the relatively long half-life and twice-daily dosing regimen, it is recommended that testing for efficacy be conducted near the end of the dosing interval at steady state. Age per se does not influence the pharmacokinetics of sotalol other than that due to the natural decline in renal function that occurs with age.

Individualization of Dosage

Sotalol is available only in oral form in the United States. The recommended initial oral dose of sotalol is 80 mg every 12 hours. In patients with relatively normal renal function, steady state is reached in 2 to 3 days. If evaluation at this dosage indicates a lack of response without evidence of excessive effects on repolarization (QT below 500 milliseconds), the dosage may be increased to 160 mg twice daily and, if necessary, to 240 mg twice daily. Some patients with life-threatening arrhythmias have required dosages of 640 mg daily. Accelerated titration regimens have been used with close monitoring without apparent increased adverse events.[120]

Modification of Dosage in Disease States

Because sotalol is mainly eliminated unchanged in the urine, the dosage must be adjusted for altered renal function.

For patients with a creatinine clearance of greater than 60 mL/minute, the usual dosing interval is every 12 hours. If the creatinine clearance (Cr Cl) is between 30 and 60 mL/minute, the recommended interval between doses is 24 hours. For patients with Cr Cl between 10 and 30 mL/minute, the interval should be every 36 to 48 hours or the usual dose halved and administered every 24 hours. The dosage for patients with Cr Cl below 10 mL/minute should be individualized. Because of the increased risk of proarrhythmia and congestive heart failure, patients with reduced cardiac output should be administered lower doses and monitored for excessive QT prolongation or worsening heart failure carefully.

Drug Interactions

Concomitant use of sotalol with agents that prolong repolarization has the potential to increase the likelihood of torsades de pointes. No pharmacokinetic interactions have been seen with sotalol and/or warfarin, digoxin, cholestyramine, or hydrochlorothiazide. Because of the β-blocking actions of sotalol, it is likely that there would be increased pharmacologic effect if the drug is combined with amiodarone, calcium channel blockers, antihypertensive agents, or antiarrhythmic agents.

AMIODARONE

Amiodarone blocks potassium, sodium and calcium channels and blocks α- and β-adrenergic receptors. It is a highly lipid-soluble compound with extremely variable and complex pharmacokinetics. It is slowly absorbed from the gastrointestinal tract, and bioavailability varies over a fourfold range.[121] Amiodarone is extensively metabolized to desethylamiodarone by CYP3A4,[122] and little, if any, is excreted unchanged in the urine. Concentrations of desethylamiodarone DEA in plasma vary from 0.4 to 2.0 times those of amiodarone during chronic therapy.[123] This metabolite has antiarrhythmic potency equal to or greater than that of amiodarone in in vitro and animal models.[124] Amiodarone is rapidly concentrated in some tissues, including myocardium, but accumulates more slowly in others, such as adipose tissue. It redistributes out of myocardial tissue while still accumulating in adipose and other tissues.[123,125] Until all tissues are saturated, rapid redistribution out of the myocardium may be responsible for early recurrence of arrhythmias after the discontinuation of therapy or rapid reduction of dosage. Because of drug accumulation in tissues, the volume of distribution for amiodarone is very large, 20 to 200 L/kg.[125] After intravenous administration, the measured half-life in plasma is from 4.8 to 68.2 hours,[126] with tissue uptake being the primary factor responsible for the decline in plasma concentration. As tissues become saturated, however, the decline in plasma levels is slow, reflecting mainly elimination and slow redistribution of drug out of adipose and muscle tissues. This leads to slow and extremely variable elimination from plasma, with half-lives ranging from 13 to 103 days at steady state.[125] It is also possible that amiodarone inhibits its own elimination after chronic therapy, contributing to the differences between half-life early in therapy to those after prolonged therapy.

Individualization of Dosage

Without a loading dose regimen, amiodarone requires several weeks to months before producing its antiarrhythmic action. Large intravenous dosages or oral loading dosages can hasten the onset of therapeutic effects. From small prospective studies, loading dosages have varied from 600 to 1400 mg daily for 2 to 21 days.[127] Large clinical trials have used a lower loading dose of 600 to 800 mg daily for 14 days.[128,129] Because of relatively rapid redistribution out of myocardial tissue, the dosage should be tapered over a period of several weeks. The usual maintenance dose varies from 200 to 600 mg daily, and because of the severe nature of adverse reactions, the lowest effective dosage should be prescribed. Patients with supraventricular arrhythmias may respond to lower dosages than those with ventricular arrhythmias, but there are many exceptions. Because of the variable pharmacokinetics and oral bioavailability, generalizations such as this may be unreliable. Some patients with extensive absorption (about 80% to 90% bioavailability) of even low doses may have the same drug exposure as a person with limited bioavailability given a high dose.

For intravenous administration, the manufacturer recommends a three-phase infusion over the first 24 hours: 150 mg over 10 minutes, followed by 360 mg over the next 6 hours, followed by 0.5 mg/minute. The drug can be continued at this rate, but monitoring of plasma concentrations is recommended. An additional 150 mg can be infused over 10 minutes for those patients who continue to have recurrent ventricular tachycardia or fibrillation or whose arrhythmia recurs during downward titration of the infusion. Concentrations of drug greater than 3 mg/mL should be infused through a central catheter to prevent phlebitis. Also, the surfactant properties of the drug alter the size of a drop of infusate, and pumps that count drops will give approximately 30% less drug than intended.

Amiodarone concentrations are usually between 1 and 2 mcg/mL during effective oral therapy.[130,131] Similar concentrations of desethylamiodarone accumulate during therapy and, although this is not proved, they are likely to contribute to antiarrhythmic efficacy. Because of extensive overlap between the range of concentrations required for arrhythmia suppression and those associated with toxicity, monitoring of plasma concentrations is of limited value. Clearly, levels of amiodarone above 3 to 4 mcg/mL for prolonged periods of time are associated with a higher incidence of adverse effects.[132]

Modification of Dosage in Disease States

Long-term oral therapy with amiodarone appears to be well tolerated hemodynamically in patients with congestive heart failure. In the Veteran's Administration trial cited, amiodarone failed to prolong life for congestive heart failure patients with arrhythmias but was associated with improved ventricular function as measured by radionuclide ejection fraction.[128]

Drug Interactions

Amiodarone interferes with the clearance of many drugs. This may involve the formation of a metabolically inactive CYP Fe (II)/metabolite complex, which has been described in animals treated with amiodarone,[133] and may explain the

reduced metabolism and unexpected accumulation of warfarin,[134] quinidine, procainamide, disopyramide, mexiletine, and propafenone[135] and the resulting bleeding, heart block, or torsades de pointes.[122,136] It does not, however, explain interaction with drugs eliminated predominantly by the kidneys, such as digoxin.[137] The elimination of other drugs may be impaired by amiodarone, and the lowest effective dosage should be sought.

IBUTILIDE

Ibutilide is available only for intravenous administration. When given over 10 minutes, it distributes rapidly in a multiexponential fashion, with the relevant component having a half-life of 2 to 12 hours (mean of 6 hours). The plasma concentration and pharmacokinetics are highly variable, and dosing is recommended on the basis of weight. The drug is mainly eliminated by oxidative hepatic metabolism, and systemic clearance is rapid (about 29 mL/minute/kg). Because formal drug interaction studies have not been performed, it is not possible to anticipate which enzymes are likely responsible for its elimination.

Individualization of Dosage

Ibutilide is administered undiluted or diluted in saline as an infusion over 10 minutes. The recommended dose is 1 mg for a patient of more than 60 kg and 0.01 mg/kg for a patient less than 60 kg. For patients whose arrhythmias have not converted by 10 minutes after completion of the first dose, a second dose of equal size can be administered. Because conversion of the arrhythmias is usually associated with peak levels, slower infusion rates are not likely to be as effective.

Because of a relatively high risk of torsades de pointes, it is essential that patients who receive ibutilide are treated in a carefully monitored environment during and at least 4 hours subsequent to treatment. The U.S. Food and Drug Administration-approved labeling recommends that skilled personnel, facilities, and medication for defibrillation or resuscitation must be readily available. Although well-controlled studies are not available, retrospective analyses indicate that pretreatment with magnesium sulfate can reduce the 3% to 4% incidence of torsades de pointes by 20% to 30%.[138]

Modification of Dosage in Disease States

Although specific studies with heart failure and renal or hepatic disease have not been conducted, current information does not indicate that any dosage adjustments should be necessary in these conditions. Patients with severe left ventricular dysfunction, however, have a higher risk of developing ventricular arrhythmias, including torsades de pointes. Because the duration of drug effect is determined by distribution, it is possible that patients with severe congestive heart failure will have decreased volumes of distribution and, hence, an exaggerated and prolonged duration of effect.

Drug Interactions

No specific drug interaction studies have been performed. Concomitant β-receptor or calcium channel antagonists apparently do not interact, although data are limited. The manufacturer's labeling warns against combining ibutilide with other drugs that prolong the QT interval. During the development of ibutilide, these drugs were discontinued for at least five half-lives prior to administration of ibutilide and were not allowed until at least 4 hours after administration.

DOFETILIDE

Dofetilide is well absorbed after oral administration and is partially metabolized by CYP3A4[139] to inactive metabolites and excreted predominantly in urine. In most patients, the elimination half-life ranges from 8 to 10 hours, but in patients with renal failure, the elimination half-life is prolonged and clearance is reduced. Dofetilide is susceptible to several drug interactions because it is metabolized by CYP3A4 (see later). It is likely that these interactions increase the risk of torsades de pointes.

Individualization of Dosage

The recommended dosage of dofetilide is 0.5 mg twice daily. Lower dosages are recommended for patients who develop excessive corrected QT interval prolongation on 0.5 mg twice daily. In the largest clinical trial, "excessive" was defined as longer than 550 milliseconds or more than 20% longer than baseline.

Modification of Dosage in Disease States

Dosage should be reduced in patients with renal disease (0.25 mg twice daily for creatinine clearance 60 to 40 mL/minute and 0.25 mg daily for creatinine clearance 40 to 20 mL/minute). Data are not available for adjustment of dosage in patients with liver disease. It is not clear whether the greater risk of torsades de pointes in women is influenced by a pharmacokinetic difference between the sexes.

Drug Interactions

The concomitant administration of dofetilide with verapamil, ketoconazole, or cimetidine (but not ranitidine) results in increased plasma concentrations of dofetilide, especially in patients with reduced renal function.[136,140] Because it is known to be a substrate for CYP3A4, there may be other important interactions with erythromycin, other macrolides, or antifungals. No interactions have been seen between dofetilide and digoxin or warfarin.

ADENOSINE

After intravenous injection, adenosine is rapidly transported into red blood cells and endothelial cells. A half-life of elimination has ranged from 1.5 to 10 seconds. The drug is rapidly metabolized in the plasma and in cells to form inosine and adenosine monophosphate. Maximal pharmacologic effects are seen within 30 seconds after injection into a peripheral intravenous line but occur within 10 to 20 seconds when administered into a central line.

Individualization of Dosage

Adenosine should be injected intravenously into a proximal tubing site and flushed quickly with saline. For adults, the initial dose is 6 mg injected over 1 to 2 seconds. If the arrhythmia persists, a 12-mg dose can be injected 1 to 2 minutes later. This can be repeated, but doses larger than 12 mg are not recommended by the manufacturer. A dosage regimen based on body weight has been proposed, with an initial dose of 50 mcg/kg incremented by 50 mcg/kg until the PSVT is terminated or side effects become intolerable.[141] Higher doses may be required for patients who have received caffeine or theophylline because of their antagonistic effects at α_1-receptors. Lower doses are recommended if the patients are receiving dipyridamole or carbamazepine.

Modification of Dosage in Disease States

Although the pharmacokinetics of adenosine are unlikely to be altered in patients with renal or hepatic disease, these patients often have electrolyte imbalances that could alter the clinical response. Although patients with congestive heart failure have not been reported to respond abnormally, heart transplant recipients appear to require one third to one fifth of the usual dose due to denervation hypersensitivity.[142]

Drug Interactions

There are several proven interactions that can increase or decrease the activity of adenosine. Dipyridamole pretreatment increases the potency of adenosine, probably because it blocks cellular uptake of adenosine.[143] Caffeine and theophylline antagonize the actions of adenosine.[144] The manufacturer cautions that carbamazepine may potentiate the actions of adenosine.

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Chapter 20

Nonpharmacologic Treatment of Tachyarrhythmias

David J. Callans and Jason T. Jacobson

CHAPTER CONTENTS

The primacy of antiarrhythmic drug therapy for the treatment of many types of tachyarrhythmias has been challenged on several fronts. First, there is increasing fear of the potential for life-threatening complications of pharmacologic therapy, particularly in patients with structural heart disease. The Cardiac Arrhythmia Suppression Trial (CAST) showed that patients treated with flecainide and encainide encountered a threefold excess mortality risk compared with placebo, despite a reduction of ambient ectopy.[1] A nonrandomized, retrospective analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) Trial[2] demonstrated that patients treated with antiarrhythmic agents for atrial fibrillation had a 2.6-fold increased risk of arrhythmic death; this excess risk was borne almost entirely by patients with a history of symptomatic heart failure. Although unusual (<1%), proarrhythmia in the form of torsades de pointes can complicate therapy with drugs that prolong cardiac repolarization, even in the absence of structural heart disease.[3] An analysis of case-specific mortality in the AFFIRM trial population showed an increased risk of noncardiovascular death (most notably pulmonary and cancer-related deaths) in patients treated with antiarrhythmic medications versus those in the rate-controlled group, despite similar rates of cardiovascular deaths in both groups.[4] Second, there is a growing appreciation for the "nuisance" side effects of pharmacologic therapy. For example, in the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Trial,[5] intolerable side effects resulting in termination of drug therapy ranged from 16% for sotalol to 43% for imipramine; additional patients developed side effects in long-term follow-up, which further limited successful therapy. These side effects add to the frustration felt by both physicians and patients. The requirement of chronic, daily therapy for a paroxysmal disorder is difficult to accept on a conceptual level. Third is the rapid development of nonpharmacologic techniques that have proved to be curative in some arrhythmia syndromes and superior to pharmacologic therapy in many others.

This chapter provides an arrhythmia-specific overview of the available techniques, current efficacy, procedural side effects, and future considerations of nonpharmacologic therapy. Although, broadly speaking, this topic could well include a discussion of surgical ablation and pacing therapy, the predominant focus is on catheter ablation. Discussion of the use of implantable electrical devices for the management of sudden cardiac death is found in Chapter 21.

CATHETER ABLATION FOR THE TREATMENT OF TACHYARRHYTHMIAS

The development of modern catheter-based ablative techniques during the 1980s and 1990s has had a remarkable effect on the treatment of many arrhythmia syndromes. Advances in these techniques have essentially eliminated the need for arrhythmia surgery (except for the treatment of atrial fibrillation), a field that was vigorous in the early 1990s. Still, as outlined later, the results of catheter ablation are syndrome specific. Although catheter ablation is first-line therapy for many paroxysmal supraventricular arrhythmias, it is largely palliative for ventricular tachycardia (VT) in the setting of structural heart disease and in evolution (albeit rapidly progressing) as a method for treatment of atrial fibrillation. Differential success rates, patient preference, and data regarding both the cost and the efficacy of ablation compared with drug therapy are important considerations in determination of the relative role of catheter ablation in specific arrhythmia syndromes.

PRACTICAL CONSIDERATIONS

The general focus of ablation therapy, either surgical or catheter based, involves selective destruction of a "vulnerable parameter" of the tachycardia circuit. Depending on the arrhythmia, this parameter can be identified electrophysiologically or anatomically. Catheter ablation requires positioning of a catheter on the basis of electrical recording and fluoroscopic, echocardiographic, or magnetic resonance imaging information (often in conjunction with three-dimensional electroanatomic mapping systems) to this critical area and the delivery of some form of energy to the tip of the catheter, resulting in focal destruction of the myocardium. Although any energy source could (theoretically) produce this lesion, catheter ablation was revolutionized with the introduction of radiofrequency energy. Catheter ablation was initially performed with direct current electrical energy, which resulted in

irregular, unpredictable lesions and significant side effects, presumably caused by barotrauma.[6]

Radiofrequency energy destroys tissue by resistive heating in the myocardium directly in contact with the distal catheter electrode.[7] Irreversible tissue death occurs at temperatures in excess of 50° C.[8] Radiofrequency lesions are homogeneous and precise, with necrotic centers 5 to 6 mm in diameter and 2 to 3 mm deep, surrounded by a hemorrhagic periphery (Fig. 20–1).[9] Two biophysical considerations fundamentally limit the size of radiofrequency lesions: (1) heat transmission diminishes by distance from the energy source to the fourth power and (2) temperatures at the catheter/myocardial surface interface >100° C lead to coagulum and gas bubble formation, preventing subsequent current delivery. Thus, the primary determinant of success is the ability to define the vulnerable parameter of the arrhythmia to an area smaller than the lesion volume possible with radiofrequency techniques. Although this is a fundamental limitation, the precision required to successfully perform catheter ablation provides an opportunity for greater understanding of the interplay of anatomic and electrophysiologic substrates for arrhythmia.[10] Nevertheless, the development of new energy sources (e.g., laser, microwave, cryoenergy, or focused ultrasound energy) or techniques (e.g., irrigated tip radiofrequency ablation) that allow the production of larger, deeper lesions could prove helpful in select applications, particularly for VT in the setting of healed myocardial infarction.

Figure 20–1 Histology of radiofrequency ablation lesion. The atrioventricular junction is seen (atrial wall is superior, coronary artery is seen in AV groove) with an ablation lesion (*arrow*) at the annulus. Note the homogeneous nature of the lesion. (From Morady F: Radio-frequency ablation as treatment for cardiac arrhythmias. N Engl J Med 1999;340:535.)

REVIEW OF THE SUCCESS OF CATHETER ABLATION BY SPECIFIC ARRHYTHMIA SYNDROME

Catheter ablation therapy is virtually always curative, with low complication rates and low cost for many supraventricular arrhythmias. Catheter-based techniques for other arrhythmias are less successful or are under development.

Catheter Ablation for Supraventricular Tachyarrhythmias

Accessory Pathway-Mediated Tachycardias

Accessory pathways are microscopic muscular bundles that connect the atrium and ventricle, providing a “bypass” of the normal conduction system (Tables 20–1 and 20–2). Manifest pathways (capable of antegrade conduction) are present in the Wolff-Parkinson-White (WPW) syndrome. Concealed pathways are not apparent on the surface electrocardiogram but can still mediate reentry. Most symptomatic arrhythmias in patients with bypass tracts are associated with a narrow QRS complex, that is, orthodromic supraventricular tachycardia (SVT)—conducted antegrade through the atrioventricular (AV) node, retrograde through the bypass tract. However, in patients with WPW syndrome, circus movement tachycardia conducting antegrade down the bypass tract and retrograde up the AV node can occur, as well as rapid accessory pathway conduction during atrial fibrillation, which may lead to cardiac arrest (estimated annual risk, 0.05% to 0.5%[11]).

The target for ablation in accessory pathway-mediated reentry is the accessory pathway itself (Fig. 20–2). The AV node is another vulnerable site, but its ablation may ultimately necessitate pacemaker therapy if antegrade bypass tract conduction fails, a phenomenon that can occur in up to 20% of patients. Accessory pathways can occur at any location around the AV rings except for the aortomitral continuity. Greater than one half of all accessory pathways are found at the left atrial free wall (62%)—the second most frequent location being the posteroseptal space (21%).[12] Right atrial free wall (13%) and anteroseptal (8%) accessory pathways are less frequently observed.[12] Right-sided pathways are ablated via a venous approach, typically at the atrial insertion of the pathway. Left-sided pathways are ablated either via a retro-

Table 20–1 Expected Success Rates for Catheter Ablation (at Referral Centers)

Tachyarrhythmia	Success (%)
Supraventricular Tachycardia	
Accessory pathway mediated	>90
Atrioventricular nodal reentry	>97
Atrial tachycardia	>80
Atrial flutter	>90
Atrial fibrillation	>75
Atrioventricular junction ablation	>97
Ventricular Tachycardia (VT)	
Idiopathic VT	>85
VT in structural heart disease	>70

Table 20–2 Indications for Catheter Ablation

First-Line Therapy in Symptomatic Patients	Potentially Helpful in Patients with Symptoms Despite Pharmacologic Therapy	Clinical Frontier Uses of Catheter Ablation
Accessory pathways	Atrial tachycardia	Polymorphic VT/VF
AV nodal reentry	Atrial fibrillation	Epicardial approach to ablation
Atrial flutter	VT in structural heart disease	
Idiopathic VT	Anatomic ablation of poorly tolerated VT	
	AV junction ablation for rate control of AF	
	Inappropriate sinus tachycardia	

AV, atrioventricular; AF, atrial fibrillation; VF, ventricular fibrillation; VT, ventricular tachycardia.

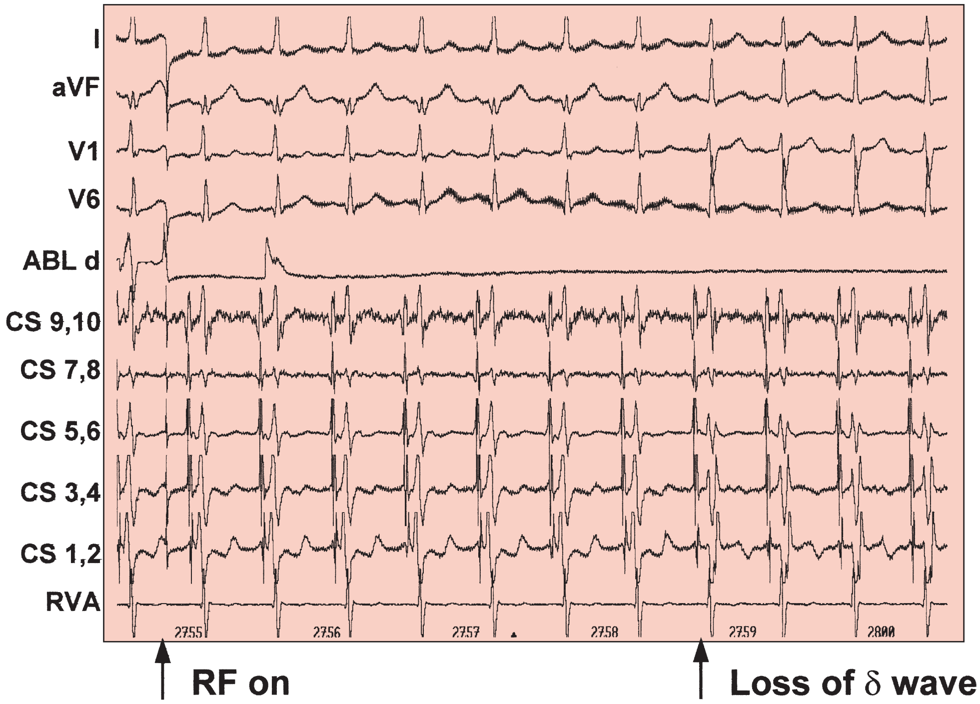

Figure 20–2 Surface ECG (I, aVF, V1, V6) and intracardiac electrograms during ablation of accessory pathway with antegrade conduction. Note the presence of preexcitation and short PR interval on the surface leads on left side of tracing (start of radiofrequency application). After 7 QRS complexes, the PR interval increases and preexcitation (δ wave) is lost. ABL d, distal ablation catheter; CS, coronary sinus catheter; RVA, RV apical catheter.

grade aortic approach or a transseptal approach to the left atrium.[13,14] A small percentage of posterior septal accessory pathways can be successfully ablated with a catheter positioned within the proximal coronary sinus, often within the middle cardiac vein or a venous malformation.[15]

Acute success rates in relatively large published series for accessory pathway ablation during the 1990s range from 71% to 100%.[13,14,16-23] Subsequent multicenter experience reports success rates independent of accessory pathway location of 93% in one study[24] and, in 1998 alone, rates of 97.7% for left-sided pathways and of 94.6% for right-sided pathways.[12] The location-dependent nature of ablation success seems to reflect differential blood flow and catheter/tissue interface contact (both of which influence lesion size),[25] as well as the anatomic complexities of the posteroseptal and anteroseptal regions. The risk of recurrence after acutely successful ablation ranges from 3% to 9%.[13,14,16-23] Recurrence after the initial loss of bypass tract function is believed to be due to temporary "stunning" caused by microvascular perfusion abnormalities in the tissue outside of the isotherm for permanent tissue death.[26] For unsuccessful attempts, the technique of epicardial mapping and ablation (see later) has been applied to persistent accessory pathways.[27] This has allowed for success with ablation from the endocardium, epicardium or both, with the aid of epicardial mapping. Complications of accessory pathway ablation are unusual and appear to be decreasing with operator experience. In the trials cited here, the incidence of major complications was 2.5%.[13,14,16-23] The most common serious complications are inadvertent AV block with paraseptal ablation and nonfatal cardiac tamponade. Thromboembolic stroke can occur with the ablation of left-sided accessory pathways, but the risk is quite low (0.1%) with procedural anticoagulation. Death has been reported with accessory pathway ablation procedures, although its incidence is approximately 0.1%.

Catheter ablation is considered appropriate first-line therapy in patients with symptomatic accessory pathway-mediated arrhythmias, particularly in young patients who want to avoid long-term pharmacologic therapy. The cost efficacy of ablation has been studied in WPW syndrome but not in the setting of concealed accessory pathways. Hogenhuis and coworkers[11] calculated a favorable marginal cost of $6600 per quality-adjusted life year gained for 20-year-old symptomatic patients.

Treatment of asymptomatic patients with incidentally detected accessory pathways is controversial. The lingering concern about the presence of a bypass tract is presentation with atrial fibrillation (which typically occurs following an episode of orthodromic tachycardia), with rapid conduction over the bypass tract causing induction of ventricular fibrillation. Viewed this way, the most important parameter is the anterograde refractory period of the bypass tract. Abrupt disappearance of preexcitation during exercise testing, or disappearance of preexcitation with type I antiarrhythmic drug infusion, identifies an accessory pathway as low risk for causing ventricular fibrillation.[28] If noninvasive testing is inconclusive, invasive testing and prophylactic ablation, if high risk characteristics are confirmed, may be appropriate in individual patients, at least in experienced laboratories.[28,29]

Atrioventricular Nodal Reentry

AV nodal reentry (AVNRT) is the most common paroxysmal supraventricular tachycardia (SVT), and the preferred vulnerable parameter is the slow pathway (Fig. 20–3). Since the development of selective slow pathway ablation strategies in the early 1990s, success rates in published series of ablation of AVNRT have ranged from 97% to 100%, with a risk of heart block of 0% to 1.5%.[22,24,30-32] The success rate in the 1998 North American Society of Pacing and Electrophysiology (NASPE) Registry was 96.2%.[12] The risk of recurrence ranges from 0% to 2%.

Although AVNRT does not cause life-threatening complications, it does cause significant symptoms in many patients. Catheter ablation is safe and highly effective therapy and is widely considered as first-line therapy in highly symptomatic patients. A cost analysis by Cheng and coworkers[33] demonstrated that catheter ablation improved quality-adjusted survival and resulted in cost savings over pharmacologic therapy in symptomatic patients with AVNRT. Alternatively, because this arrhythmia occurs most frequently in young patients, some experts suggest that ablation should be pursued only after the failure of relatively benign pharmacologic therapy such as digitalis or low-dose β-blockers rather than exposing them to a 1% risk of inadvertent heart block requiring life-long pacing therapy. In our experience, however, β-blocker therapy is often poorly tolerated in young patients.

Atrial Tachycardia

The ablation experience for atrial tachycardia is more limited due to the relative infrequency of this arrhythmia and the lack of consistent induction in the electrophysiology laboratory.[34] The vulnerable parameter for atrial tachycardia is the focal site of origin in the atrial myocardium, recognized by the site of earliest atrial activation during tachycardia. Although it was previously believed that atrial tachycardia arose consistently from the right atrium in adults, particularly along the crista terminalis,[34] the frequency and importance (e.g., as a source for focal atrial fibrillation, see later) of left atrial tachycardia are now recognized.

Contemporary series of atrial tachycardia ablation report acute success rates of 80% to 100% with rare complications and a recurrence risk of 0% to 25%.[35-39] The 1998 NASPE Registry reported a success rate of 70.2% and a complication rate of 2.99%.[12] These success rates may overpredict the true efficacy of catheter ablation in this setting for two reasons,

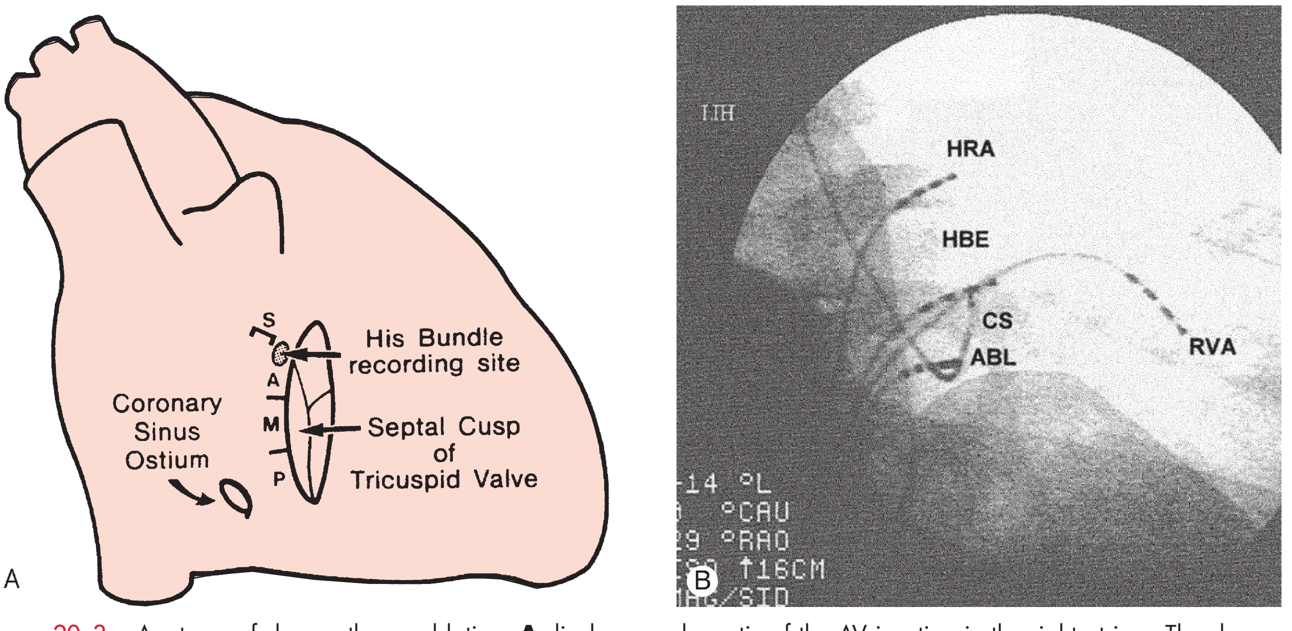

Figure 20–3 Anatomy of slow pathway ablation. **A** displays a schematic of the AV junction in the right atrium. The slow pathway is usually ablated just anterior to the CS ostium, at the posterior septal isthmus. **B** displays the right anterior oblique fluoroscopic view of ablation catheter location. A, anterior septal isthmus; ABL, ablation catheter; CS, coronary sinus catheter; HBE, His bundle catheter; HRA, high right atrial catheter; M, midseptal isthmus; P, posterior septal isthmus; RVA, right ventricular catheter; S, septum. (**A,** Redrawn from Jazayeri MR, Hempe SL, Sra JS, et al: Selective transcatheter ablation of the fast and slow pathways using radiofrequency energy in patients with atrioventricular nodal reentrant tachycardia. Circulation 1992;85:1318-28.)

however. First, these series report the success rate in patients who have uncomplicated diagnostic studies and reproducible atrial tachycardia that can be mapped. A true intention-to-treat analysis would probably show a lower success rate because mapping and ablation cannot be performed without either spontaneous or inducible sustained atrial tachycardia. Second, atrial tachycardia occurring in the setting of repaired congenital heart disease, often relating to the surgical incision, may be much more difficult to approach with catheter ablation. Nevertheless, Kalman and coworkers[40] reported success in 15 of 18 acute patients (21 of 26 tachycardias) with postsurgical "incisional" tachycardia.

Because of the unpredictable nature of atrial tachycardia and the lower degree of procedural efficacy, catheter ablation is typically performed only after pharmacologic therapy is unsuccessful. Primary ablation therapy does not apply to multifocal atrial tachycardia, but this arrhythmia is occasionally treated with AV node ablation (see later).

Inappropriate sinus tachycardia is a nonparoxysmal automatic tachycardia with a P wave consistent with sinus node origin and an exaggerated rate response to endogenous catecholamines.[41] There is limited published experience, which initially suggested that lesions delivered intentionally to the sinus node region may control symptoms in up to 90% of patients[42]; recurrent symptoms are common, however, and often unrelated to rhythm abnormalities. Complications of sinus node modification include symptomatic bradycardia that requires pacing in 10% of patients. Subsequent experience suggests that ablation guided by intracardiac echocardiography may improve safety and efficacy.[43,44]

Atrial Flutter

Typical atrial flutter is caused by macroreentry in the right atrium; the reentrant impulse is anatomically constrained to the narrow "isthmus" of tissue between the tricuspid annulus and the inferior vena cava. This isthmus forms the vulnerable parameter and the target for atrial flutter ablation.[45] Several studies have demonstrated the superiority of an anatomic approach to atrial flutter ablation, reducing recurrence rates from 25% to 5% to 10%.[46-48] In this approach, bidirectional isthmus conduction block is used as an endpoint rather than termination and subsequent inability to induce atrial flutter (Fig. 20–4). Acute success rates in these series were greater than 90%, and complications are rare. The 1998 NASPE Registry reported an acute success rate of 86% with a recurrence rate of 13%.[12] One limitation of ablation for atrial flutter is the high incidence of atrial fibrillation (up to 26%) after successful procedures,[49,50] raising suspicion about the potential proarrhythmic effect of ablation. However, Natale and colleagues[51] performed a randomized trial of primary ablation versus antiarrhythmic therapy for patients with atrial flutter without atrial fibrillation. The ablation strategy not only provided better arrhythmia control and cost less than the pharmacologic strategy, but also provided greater freedom from atrial fibrillation in follow-up. These observations, as well as the high-efficacy and low-risk profile of catheter ablation in this setting, argue that ablation is appropriate first-line therapy for symptomatic patients with atrial flutter.

Atypical atrial flutter (i.e., not cavotricuspid isthmus dependent; especially left atrial flutter) is an entity most

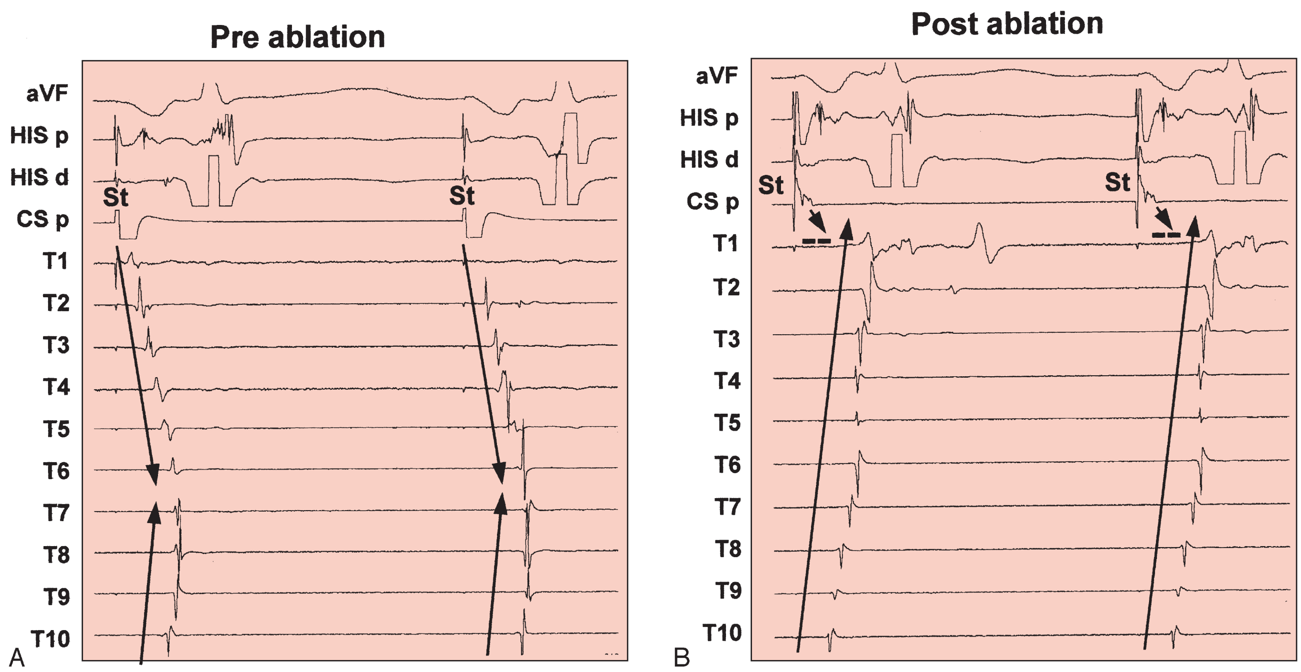

Figure 20–4 Activation sequence around the tricuspid annulus before and after cavotricuspid isthmus ablation for atrial flutter. A circular mapping catheter is placed on the atrial side of the tricuspid valve annulus. T10 is the proximal electrode that sits at the superior annulus; T1 is the distal electrode that sits at the inferolateral annulus. Part **A** shows that during pacing from the coronary sinus (CS) before ablation, activation spreads in two directions around the tricuspid valve (note the "Christmas tree" pattern of activation on the mapping catheter around the TV annulus). After ablation, activation is blocked **(B)** at the ablation line (which is just medial to T1) and spreads in a counterclockwise direction around the annulus (from T10 to T1). aVF, surface ECG lead; CS p, proximal coronary sinus catheter; HIS p and HIS d, proximal and distal His catheter.

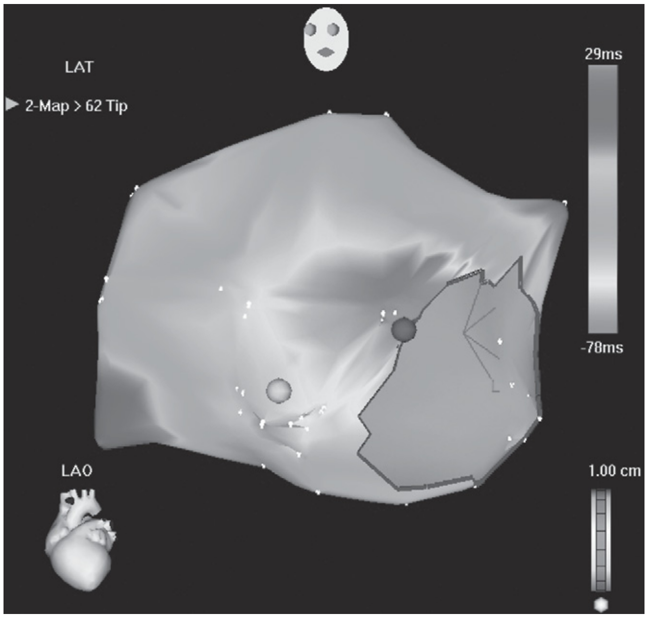

Figure 20–5 (*See also Color Plate 20–5.*) Three-dimensional electroanatomic activation map of atrial tachycardia originating from the mitral annulus. Right anterior oblique view of left atrial map. The earliest activation is indicated in *red*; latest in *purple*. Radiofrequency ablation terminated this tachycardia with one application (*red dot*). The *yellow dot* is the location of the His bundle in the right atrium.

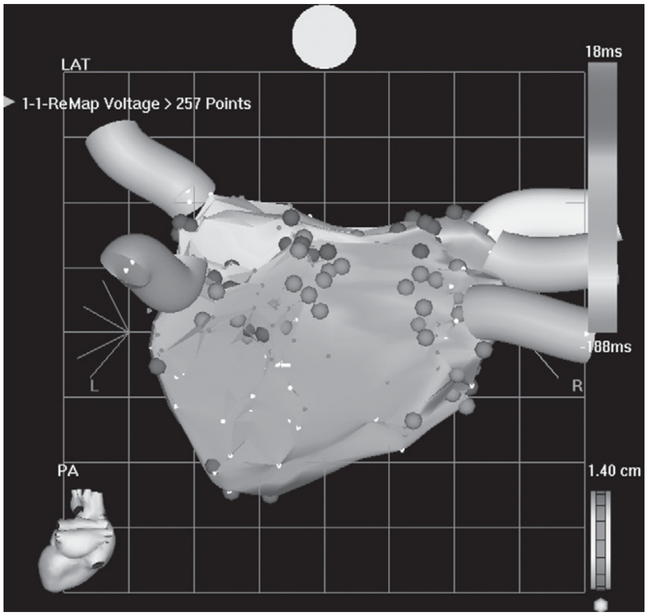

Figure 20–6 (*See also Color Plate 20–6.*) Segmental pulmonary vein isolation. An electroanatomic map of the left atrium is shown in a posteroanterior view. The left superior and inferior pulmonary veins are indicated in *purple and blue on the left;* the right superior, middle, and inferior pulmonary veins are indicated in *yellow, pink, and orange on the right.* The *red dots* indicate full power radiofrequency (RF) applications, whereas the *pink dots* indicate low power, short duration RF applications near the esophagus.

frequently seen in patients with atrial scarring, either due to coexisting structural heart disease or after cardiac surgery.[52] A more contemporary etiology of left atrial flutter is prior ablative therapy of atrial fibrillation (see later).[53-55] Using a transseptal approach and modern mapping systems (Fig. 20–5), many of these arrhythmias can be successfully ablated.[52,55]

Atrial Fibrillation

Since the realization that atrial fibrillation is often initiated by ectopic depolarizations originating in the pulmonary veins near their attachment with the left atrium,[56] the evolution of ablation for the treatment of this ubiquitous arrhythmia has been rapid and significant. Throughout the discovery process, a conceptual debate has raged over what the target of ablation should be.

"Trigger ablation" refers to the procedure that targets the atrial ectopic foci that fire during the atria's vulnerable period (i.e., heterogeneous repolarization), leading to atrial fibrillation. The entity of focal atrial fibrillation is a syndrome of frequent paroxysms of atrial fibrillation in young patients without structural heart disease; this syndrome is "triggered" by rapid but uniform atrial tachycardia.[57,58] Atrial triggers for focal atrial fibrillation are most often located within the pulmonary veins and have been successfully ablated there,[56,58] but other smooth left atrial sites, the crista terminalis, Eustachian ridge, and superior vena cava, have also been implicated. Pulmonary vein ablation has evolved from a technique aimed at ablating the site of focal discharge from within the vein to the electrical isolation of the vein just outside its ostium. This has been necessitated by the development of pulmonary vein stenosis after ablation within the vein and also by the conceptual risk of leaving behind potentially arrhythmic proximal pulmonary venous tissue.[59-61] Isolation of the veins is usually achieved by ablating a segment of the ostium (Fig. 20–6)[62,63] without totally encircling it, thereby minimizing the risk of stenosis. Ablation lesions are created encircling the pulmonary vein until it has been electrically isolated.

"Substrate ablation" refers to targeting the atrial muscle that is responsible for the maintenance of atrial fibrillation after initiation by an ectopic beat. The area felt to be most important as a substrate is the posterior left atrium, demarcated by the pulmonary vein ostia. The creation of wide, encircling RF lesions around the pulmonary veins (wide area catheter ablation) not only blocks the initiating ectopic beats but also appears to modify the substrate.[54,64,65] With this approach, electrical isolation of the pulmonary veins is not the goal and is not frequently achieved. Another approach aimed at modifying the substrate for AF has been proposed by Nadamanee and colleagues.[66] This technique involves mapping both atria in search of complex fractionated (multipeaked or continuous) electrograms that are believed to be the "anchor points" for the wavelets that drive AF. These investigators found these electrograms in nine areas throughout both atria and report a success rate comparable with both segmental pulmonary vein isolation and wide area catheter ablation. Finally, mapping of the intrinsic cardiac nervous system and targeting of ablation lesions to modify vagal effects on the atrium have also been suggested.[67,68]

Despite different approaches to the ablation of AF, success rates seem comparable among all techniques (85% to 91%

freedom from symptomatic AF with or without antiarrhythmic drugs)[59,65,66,69,70] and randomized comparisons of wide area catheter ablation and pulmonary vein isolation are few and somewhat conflicting.[54,71] Whereas AF ablation was initially reserved for patients with paroxysmal AF with structurally normal hearts, those with persistent AF and concomitant heart disease (e.g., cardiomyopathy, valvular disease, and so on) have also demonstrated benefit from the procedure,[69] although at decreased rates of success. Most patients are considered candidates after initial failure of antiarrhythmic drug therapy. In addition, various series have inconsistent approaches to the need for "adjuvant" antiarrhythmic drug therapy after less than completely successful ablation. It remains to be seen which approach will produce the most benefit for specific subsets of patients.

Results of many studies show efficacy of ablation for control of symptomatic AF, but caution must be exercised when interpreting the data. Most studies report a primary endpoint of symptomatic recurrence of AF and perform limited outpatient monitoring for arrhythmias after ablation. Although the population of patients included in these series are highly symptomatic, it is becoming clear with more intensive monitoring that even symptomatic patients can have frequent episodes of asymptomatic AF, both before and (more frequently) after catheter ablation.[72] This phenomenon was also found by Karch and coworkers[71] in a randomized comparison of pulmonary vein isolation and wide area catheter ablation for the treatment of AF. Despite a significant freedom from symptomatic recurrence in both groups (54% for wide area ablation and 82% for pulmonary vein isolation), 7-day Holter monitoring at 6 months showed atrial tachyarrhythmias in 58% and 34% of patients in each group, respectively. These results suggest that a patient's perception of AF may change after ablation. More importantly, these data caution against discontinuing anticoagulation after ablation in patients who have successful control of their symptoms without the use of extensive monitoring to confirm arrhythmia control.

Ablation in the left atrium carries some risk. In a world survey of AF ablation,[59] Cappato and associates found a 0.94% incidence of CVA/TIA and a 1.63% incidence of pulmonary vein stenosis (about one half of which cases were symptomatic). A dreaded complication first noted by cardiothoracic surgeons performing ablation for AF in the operating room[73] and most recently by electrophysiologists performing percutaneous AF ablation[74] is atrioesophageal fistula. This complication usually manifests 1 to 4 weeks after the procedure and can occur with symptoms of cryptogenic stroke, endocarditis, or hematemesis. Patients may develop systemic air emboli (especially if subjected to esophagoscopy), gastrointestinal bleeding, or mediastinitis. Although the phenomenon itself is extremely rare, the mortality rate is high (50%). Treatment hinges on immediate detection and surgical correction. New intraprocedural imaging techniques, such as intracardiac echocardiography and barium swallow, have been used to attempt to eliminate this complication.

Atrioventricular Junction Ablation for Ventricular Rate Control

There is growing evidence to suggest that uncontrolled ventricular rates during atrial fibrillation frequently cause tachycardia-related myopathy (see Chapter 24).[75] This is of special concern in the presence of preexisting structural heart disease because these patients are at high risk of complications from antiarrhythmic therapy and are less likely to tolerate the negative inotropic effects of AV node-blocking agents. Catheter ablation of the AV junction was the first routinely successful strategy using radiofrequency energy; even in early published series, acute success rates were 98% to 100%.[76,77] In the 1998 NASPE Registry, the acute success rate was 97.6% with a 3% risk of recurrence.[12] Randomized comparisons of ablation with medical therapy demonstrated better symptomatic control and improvement in left ventricular (LV) function in patients with severe symptoms.[78,79] Despite this success, there are two important limitations to AV junction ablation. The first involves the requisite pacemaker dependence for ventricular rate support and the potential complications that result from pacing system failure. In recent years, it has become clear that right ventricular (RV) pacing can be deleterious, especially in patients with compromised LV function. RV pacing produces dyssynchronous ventricular contraction analogous to that seen in patients with left bundle branch block. In response, the PAVE (ACC 2004) study investigated the prophylactic implantation of biventricular pacemakers in patients undergoing AV junction ablation. This study found that patients treated with a biventricular pacemaker performed better on a 6-minute walk test and that LV ejection fraction was preserved, as opposed to a 4.2% decrease in patients treated with RV pacing after ablation.

Catheter Ablation for Ventricular Tachyarrhythmias

Idiopathic Ventricular Tachycardia

There are several distinctive syndromes of VT that occur in patients without structural heart disease that are recognized by their electrocardiographic characteristics: right ventricular (RV) outflow tract VT and idiopathic LV (midseptal) tachycardia (see Tables 20–1 and 20–2). Less commonly, idiopathic VT can arise from other sites in the right or left ventricle. RV outflow tract tachycardia has a left bundle branch block morphology and inferior axis on the 12-lead surface ECG, and usually manifests as salvos of nonsustained VT precipitated by exercise or emotion. It is usually mapped to just below the pulmonary valve on the septal aspect of the RV outflow tract.[80] Series of catheter ablation have demonstrated acute success rates in excess of 85% with low rates of complications,[80-82] although procedure-related death has been reported.[82] One reason for lack of efficacy of RV ablation in some patients with this syndrome is a "mimic" VT with an inferior axis but earlier precordial transition (before V_3), which indicates an LV outflow tract[83] or epicardial origin.[84] LV midseptal VT is distinguished by its right bundle branch block, left superior axis ECG morphology. LV mapping localizes this tachycardia to the inferior aspect of the midseptum; often, Purkinje fiber activation precedes local ventricular activation at the site of origin both in sinus rhythm and during VT.[85] Although the published experience is limited by the relatively infrequent incidence of this arrhythmia, several studies have shown acute success rates of 85% to 100% without procedural complications.[83,84,86] Because of the efficacy of catheter ablation of the two predominant forms of idiopathic VT, as well as its relatively low risk, it is recommended for patients with persistent

symptoms despite drug therapy (typically β-blockers and calcium channel antagonists) or when the individual patient prefers ablation therapy to drug therapy. By extension, although without the support of published experience, catheter ablation may be effective in treating idiopathic VT that does not fit these well-described clinical syndromes.

Ventricular Tachycardia in Patients with Structural Heart Disease

Sustained, monomorphic VT can complicate several forms of heart disease, including coronary heart disease, nonischemic dilated cardiomyopathy, RV dysplasia/cardiomyopathy, and sarcoid heart disease. The most frequent and well-understood anatomic substrate for VT is healed myocardial infarction—in which slow, discontinuous conduction in the surviving border zone of the infarct allows the establishment of stable reentrant circuits.[87] Sites of arrhythmia origin are recognized by low-amplitude, fractionated endocardial electrograms, an electrophysiologic marker for the slow conduction necessary for reentry (Fig. 20–7).[88] Similar endocardial electrograms can guide catheter mapping in other forms of heart disease.[89,90] In RV cardiomyopathy, sarcoid-related cardiomyopathy and idiopathic dilated cardiomyopathy, electrogram abnormalities are typically localized to perivalvular areas; in dilated cardiomyopathy, epicardial electrogram abnormalities sometimes predominate.[91]

Radiofrequency catheter ablation has proved to be modestly effective in a minority of well-selected patients with VT in the setting of healed infarction.[92-94] Several factors limit the success of VT ablation in this setting.[10] First, although patients often have a "dominant," frequently occurring clinical morphology, the anatomic substrate for VT is such that many other morphologies are usually inducible or will develop over time. Even after the successful ablation of a dominant morphology, the VT substrate remains largely unaltered, and VT ablation is not viewed as a curative procedure. Second, the areas critical to the VT circuit are sometimes located deep within infarct scar; radiofrequency lesions are not able to penetrate deeply into scarred myocardium.[9] Newer technologies for energy delivery, such as irrigated radiofrequency, help to overcome this limitation.[95] Third, traditional methods for VT localization require prolonged mapping during VT, a condition that many patients with poor ventricular function cannot tolerate. Largely anatomically directed linear ablation lesion techniques (Fig. 20–8) have proved to be helpful in poorly tolerated, unmappable VT.[96] The prognosis for patients who present with sufficiently frequent VT episodes to be considered for ablation is dismal, most likely reflecting the advanced stage of ischemic cardiomyopathy. Data from ablation series range from 12% to 30% mortality at 36 to 40 months, to 51% at 5 years.[97-99]

With these limitations in mind, the efficacy reported in published trials for VT ablation ranges from 67% to 96%.[92-94,100-102] The 1998 NASPE Registry reported a disappointing success rate of 59%, with an incidence of complications of 3.8%.[12] It is important to remember the highly selected nature of the patient population, estimated at approximately 10% of the total population with sustained VT.[92] An intention-to-treat analysis demonstrated successful ablation of only 58% of patients suspected to be candidates for VT ablation; this success rate rose to 71% after the inclusion of multiple procedures.[94] The risk of these procedures is higher than that in other situations because of the left-sided approach (particularly in the setting of atherosclerotic

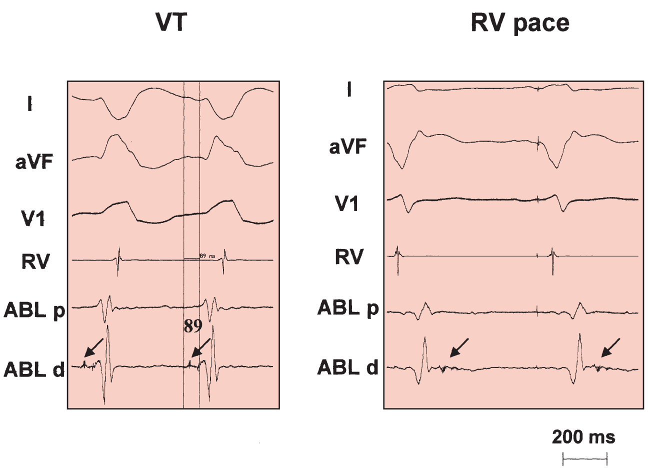

Figure 20–7 Electrogram (EGM) from area of slow conduction in VT circuit. *Left:* Recording during VT. The ablation catheter (ABL d) is in the left ventricle at the exit of the VT circuit. Note a low voltage presystolic deflection that is 89 msec before the onset of the surface QRS and before the larger component of the EGM. *Right:* The same recording site during right ventricular pacing. The larger component of the EGM now precedes the low-voltage deflection, indicating slow conduction into scar during RV pacing. ABL p and ABL d, proximal and distal ablation; EGM I, aVF, V1, surface ECG leads; RV, RV EGM.

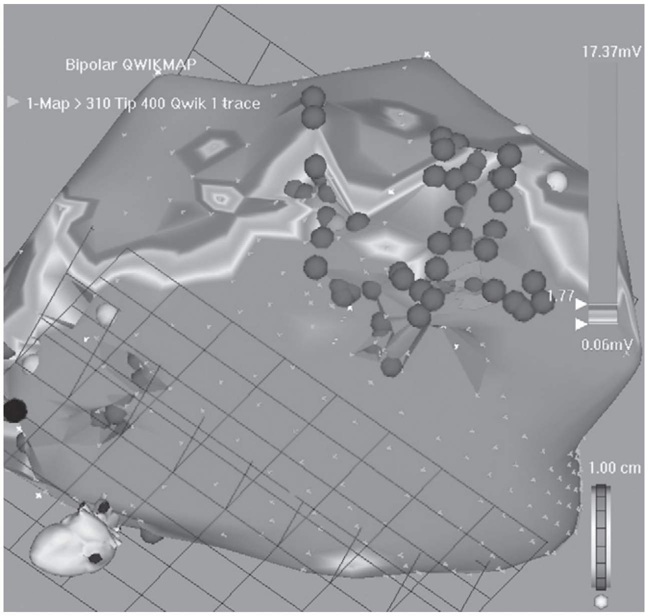

Figure 20–8 (*See also Color Plate 20–8.*) Linear ablation of scar-related ventricular tachycardia. Inferior view of left ventricle. Myocardial scar is displayed in *red* (low voltage). Normal myocardium is displayed in *purple* (normal voltage). Two lines of RF lesions (*red dots*) are seen at the base of the LV, extending from deep within the scar, across the border zone to normal myocardium.

disease) and the general condition of the patients. Serious complications occur in approximately 2% of patients and include stroke and death.[92-94,100-102] Although the VT that was targeted for ablation recurs in fewer than 10% of cases in follow-up, the occurrence of a new VT morphology is likely. For this reason, at present we recommend ICD back-up in all patients who undergo VT ablation.[103]

The patients who appear to benefit most from this procedure are those with incessant VT or who have received multiple defibrillator shocks for relatively slow VT that does not respond to adjuvant antiarrhythmic drug therapy or antitachycardia pacing. Analysis of this strategy showed that it significantly improved patients' quality of life.[104] Some investigators also apply VT ablation as primary therapy to patients who present with well-tolerated VT.[102] In our experience, however, presentation with well-tolerated VT does not predict that recurrent VT episodes will also be tolerated, particularly after ablation.[103,105]

Patients with nonischemic dilated cardiomyopathy and VT may also benefit from radiofrequency ablation.[91,106] Whereas most VT in these patients is reentrant in etiology, bundle branch/fascicular and focal VT may also occur.[91,107] Bundle branch reentrant (BBR) VT uses the left and the right bundle branches in a circuit that can be easily treated by ablation of the right bundle branch.[108] Although BBR VT is seen in patients with dilated cardiomyopathy, intramyocardial reentrant VT is the predominant form in this population. The methods of ablation used for patients with VT in the setting of healed infarction have been applied to VT in dilated cardiomyopathy with similar (albeit somewhat lower) success.[91,106] Some of these patients may have VT circuits or foci that are located on the epicardial surface of the heart, and with a technique recently described by Sosa and colleagues[109] to access the pericardium percutaneously, these VT may be successfully ablated in the electrophysiology laboratory.[91] Despite these advances, ablation is considered as adjuvant therapy to ICD therapy in patients with VT in the setting of structural heart disease.

Ventricular Fibrillation and Polymorphic Ventricular Tachycardia

Due in part to the success of ablation for atrial fibrillation, the trigger hypothesis of arrhythmia initiation has been applied to the treatment of ventricular fibrillation (VF) with ablative techniques. Selected patients with VF and polymorphic VT (PMVT) due to varied etiologies such as Brugada syndrome and long QT syndrome,[110] post-infarction,[111] and idiopathic VF[112] have achieved control of VF by mapping and ablation of the triggering premature ventricular beats that initiate their tachyarrhythmia. These premature beats most often originate from the Purkinje system, but may also arise from the right ventricular outflow tract.[110,111,112] The literature is limited to case reports and case series at this time and, therefore, ICD implantation remains the preferred therapy—whereas ablation can be considered in patients with frequent ICD shocks in the setting of uncontrolled arrhythmia.

SUMMARY

Developments in nonpharmacologic therapy have eclipsed the results possible with antiarrhythmic drugs in many arrhythmia syndromes. Catheter ablation therapy is highly effective in a variety of supraventricular arrhythmias. Extension of this success to the majority of patients with VT and VF, particularly in the setting of structural heart disease, awaits technologic enhancements as well as improvements in understanding of the arrhythmia substrate.

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Chapter 21

The Role of Implantable Cardioverter-Defibrillators in Primary and Secondary Prevention of Sudden Cardiac Death

Rishi Arora, Daniel R. Frisch, and Alan H. Kadish

CHAPTER CONTENTS

SUDDEN CARDIAC DEATH—THE SCOPE OF THE PROBLEM

Sudden cardiac death (SCD) causes more than 400,000 deaths annually in the United States and accounts for more than one half of all deaths from coronary artery disease.[1] SCD has been defined as sudden, unexpected death from a cardiac cause within a short time period (≤1 hour) after the onset of cardiac symptoms, or as death from a cardiac cause occurring outside of a hospital, in an emergency department, or on arrival to a hospital. Approximately two thirds of these deaths occur in the out-of-hospital setting, with the vast majority of these deaths considered to be the result of a ventricular tachyarrhythmia.[2]

Of concern is the fact that despite a decline in overall cardiovascular disease mortality over the last decade, the proportion of cardiac deaths attributable to SCD continues to rise.[1] Such a trend is believed to, at least partially, reflect the increased prevalence of heart disease and its risk factors in the U.S. population and improvement in the care of other cardiac conditions. Given that SCD claims more lives every year than AIDS, breast cancer, lung cancer, and stroke combined, serious attempts have been made over the last 2 decades as part of a major public health initiative to identify and treat populations at risk for SCD. To date, attempts to reduce rates of SCD have focused primarily on patients with coronary heart disease (CHD) and left ventricular dysfunction because these patients are known to have high rates of arrhythmias and SCD. However, a major limitation of currently available high-risk markers of SCD (such as CHD and left ventricular dysfunction) is that they can be used to identify only a small percentage of at-risk patients. The majority of patients who succumb to SCD do not belong to any currently defined high-risk category (Fig. 21–1),[3] as defined by the presence of coronary artery disease, reduced left ventricular systolic function, congestive heart failure, or earlier cardiac arrest.

The survival of a patient with SCD due to ventricular fibrillation is critically dependent on the time to defibrillation,[4,5] with greatest survival rates being seen with successful defibrillation within the first 4 minutes of cardiac arrest. Despite dramatic improvements in emergency response services in the industrialized world over the last few decades, it is unfortunate that, depending on the arrhythmia at presentation (i.e., ventricular fibrillation, electromechanical dissociation, or asystole), only 1% to 25% of all patients with SCD survive to discharge after hospitalization.[4] These odds have made the implantable cardioverter-defibrillator (ICD) the preferred approach for secondary, as well as for primary, rescue therapy for SCD. This practice is supported by continued improvement in device technology and multiple clinical trials that demonstrate improved outcomes with an ICD as compared with pharmacologic therapy in patients at risk of sudden cardiac death. Although the ICD does not prevent malignant ventricular arrhythmias, it does reverse them promptly when they occur, with efficacy rates as high as 99%.

ADVANCES IN ICD TECHNOLOGY AND IMPLANTATION TECHNIQUES

ICD technology has come a long way since Mirowski reported the first implantation of an epicardial defibrillator via a thoracotomy in 1980. The majority of such epicardial implants were for high-risk survivors of sudden cardiac death. The introduction of endocardial implantation techniques and transvenous defibrillation leads in the early 1990s made more widespread prophylaxis a reality, as operative morbidity and mortality rates rapidly declined from a 3% mortality risk for epicardial implants to a less than 1% incidence of significant complications for the latest generation of transvenous ICDs.

ICD generators have also decreased significantly in size since the earlier models. First-generation ICD generators were large (160 to 190 cm^3) and heavy (>200 g), necessitating

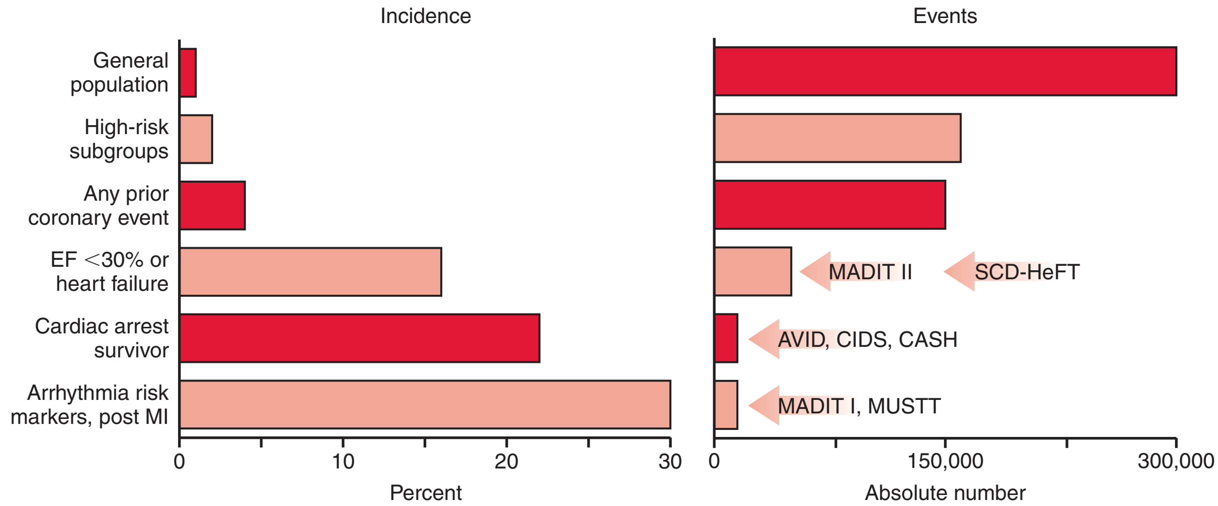

Figure 21–1 Relation between population and subsets, incidence of sudden cardiac death, and total population burden for each group. With increasing incidence, based on subgroup profiling, there is a decreasing proportion of the total sudden death burden. This relates to the population impact of the outcomes of implantable cardioverter-defibrillator (ICD) trials. (From Myerburg RJ, Interian A, Jr, Mitrani RM, et al: Frequency of sudden cardiac death and profiles of risk. Am J Cardiol 1997;80:10F-19).

implantation in the abdominal wall, either subcutaneously or under the rectus muscle. The current generation of devices averages 35 cm^3 and can be implanted in the prepectoral, subcutaneous fascia in most cases.

ICDs originally only delivered shocks to rescue from ventricular tachycardia or ventricular fibrillation. These devices also treat bradycardia with single- and dual-chambered rate-adaptive pacemakers. More contemporary devices also offer concomitant left ventricular pacing (resynchronization therapy). Newer generation devices have added capabilities for transtelephonic interrogation of detection criteria, therapy parameters, and other diagnostic information. Other relatively recent improvements include additional therapies specific for ventricular tachycardia, improved tachycardia discrimination algorithms, antitachycardia and bradycardia pacing, noninvasive programmed stimulation, storage of high rate counters or electrograms, and biphasic waveform shocks.

ICD USE IN SECONDARY PREVENTION OF SCD

The ICD is highly effective in terminating VT/VF and in aborting SCD. Initial uncontrolled studies suggested that an ICD reduced SCD rates to well below those seen in historical controls.[6] These initial uncontrolled observations provided the basis for performing more rigorous, randomized controlled trials to determine the true benefit of an ICD for ssecondary prevention.

Because the ICD would not be expected to reduce death from heart failure or noncardiac causes (but may in effect shift the cause of death from SCD to non-SCD) and because of the potential to misinterpret the mechanisms responsible for apparent sudden deaths, the only valid primary endpoint for such trials was believed to be total mortality. Nonetheless, sudden arrhythmic death remains an important secondary endpoint in such studies, especially because the ICD exerts its beneficial effects on mortality primarily by effective treatment of ventricular tachyarrhythmias.

Three randomized secondary prevention trials (Table 21–1) comparing ICDs with pharmacologic antiarrhythmic agents were reported from 1997 to 2000. There were subtle differences among the studies in the patient entry requirements and treatments assigned in each of these trials (discussed later).

In summary, a significant mortality benefit with an ICD was noted in the Antiarrhythmic Drug Versus Defibrillator (AVID) trial,[7] and nonsignificant trends toward reduced mortality rates with an ICD were noted in the Cardiac Arrest Survival in Hamburg (CASH) and the Canadian Implantable Defibrillator Study (CIDS) trials.[8,9] The latter two trials are believed to have been underpowered to detect a significant difference of the magnitude observed. However, both of these trials were found to have contributed to more deaths when a meta-analysis of all three studies was performed; this was, in part, due to longer follow-up in CASH and CIDS as compared with AVID.[10] Nonetheless, this meta-analysis found a significant 25% reduction in mortality rate with an ICD compared with amiodarone therapy (hazard ratio 0.75, 95% confidence interval [CI] 0.64 to 0.87) that was entirely due to a 50% reduction in sudden death (hazard ratio 0.50, 95% CI 0.34 to 0.62). The absolute reduction in all-cause mortality was 7% at 2 years, meaning that 15 patients needed to be treated to prevent one death. Importantly, subgroup analysis has suggested that some patients who have survived a cardiac arrest, such as those >65 years or with well-preserved left ventricular function, may not have so great a benefit from ICD therapy. Although the data suggesting lower mortality in patients who receive an ICD are clear, there are many patients who experience a cardiac arrest in whom less aggressive medical therapy may be appropriate because of an overall poor prognosis or comorbid conditions.[11]

Table 21–1 Secondary Prevention Trial Outcomes

Trial	Randomized to ICD w/Implant (%)	Receiving Amiodarone (%)	Follow-Up Duration (mo)	2-Yr Mortality Drug Rx (%)	2-Yr Mortality ICD (%)	Hazard Ratio (ICD)
AVID	98	85 (2 yr)*	18	24	15.8	0.73
CIDS	95	80 (3 yr)	36	20.97	14.75	0.70
CASH	100	90 (study duration)	57	22	12	0.61

*At stated follow-up information was provided.
AVID, Antiarrhythmics Versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; ICD, implantable cardioverter-defibrillator.
Modified from Buxton AE: Results of clinical trials of automatic external defibrillators and implantable cardioverter-defibrillators in patients at risk for sudden death. In Zipes DP, Jalife J (eds): Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, WB Saunders; 2004, pp 901-9).

ICD USE IN PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

Although ICD implantation for secondary prophylaxis has gained widespread acceptance in the medical community, indications continue to evolve for use of the ICD for primary prevention for SCD. Most of the large-scale studies that have been performed for primary prevention have been in patients with known coronary artery disease with abnormal left ventricular (LV) systolic function, although studies have begun to address patients with nonischemic dilated cardiomyopathy (NIDCM).

Patients with infarct-related cardiomyopathy (IRCM) have been targeted by ICD trials because of the known risk of SCD in this patient population. Acute, as well as chronic ischemic, states are known to be associated with an increased risk of SCD. Evidence for this comes, in part, from the Framingham cohort, in which a history of CHD was found to impart a 3- to 12-fold increase in risk of sudden death, with other conventional CHD risk factors also imparting varying degrees of risk. Beyond the presence of coronary artery disease, several additional risk factors have been used to stratify the likelihood of SCD. Three risk factors that deserve special mention include (1) reduced left ventricular ejection fraction (LVEF); (2) presence of nonsustained ventricular tachycardia (NSVT); and (3) inducibility of ventricular tachycardia/ventricular fibrillation (VT/VF) during electrophysiology study (EPS).

Left Ventricular Ejection Fraction

Left ventricular dysfunction, as measured by the left ventricular ejection fraction (LVEF), is one of the most powerful predictors of mortality at 6 months and 1 year (Fig. 21–2) after acute MI.[12] The higher rate of mortality includes an increase in SCD. Among patients receiving standard therapy, such as ACE inhibitors, the rate of SCD was 1.4% at 1 year in the GISSI-Prevention trial of patients who generally had an LVEF > 40%,[13] approximately 8% at 1 year in the TRACE trial of patients with an LVEF ≤ 35%,[14] and 9.4% at 20 months in the MADIT II trial of patients with an LVEF ≤ 30%.[15] In the ESVEM trial, LVEF was the single most important predictor of arrhythmic death or cardiac arrest in patients with life-threatening arrhythmias who were treated with antiarrhythmic drugs. Of the 486 patients enrolled over a 6-year follow-up, 285 had an arrhythmia recurrence. Patients with an LVEF >40% had a 5% risk of developing a malignant arrhythmia, whereas for each decrease of 5% in LVEF, the risk of cardiac arrest or arrhythmic death increased by 5%.[16] Left ventricular dysfunction has, therefore, been an entry criterion for every major clinical trial that has attempted to evaluate the efficacy of an ICD for primary prevention of SCD, in both the presence and absence of coronary artery disease (i.e., IRCM as well as NIDCM).

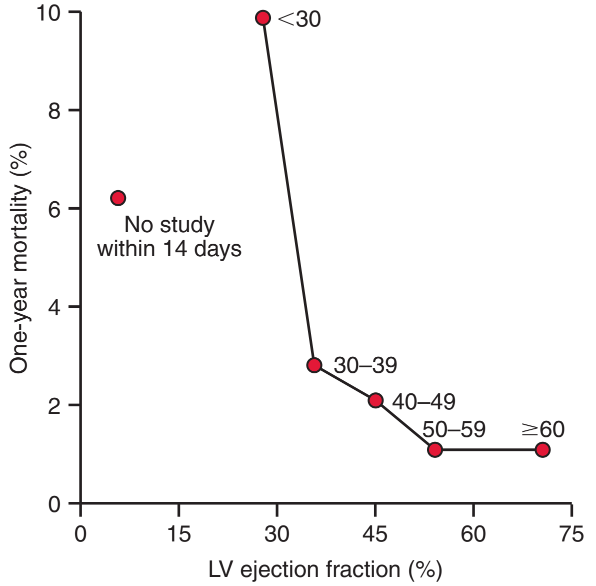

Figure 21–2 LVEF predicts 1-year mortality after MI. Among 3197 patients enrolled in the TIMI II trial, the 1-year mortality correlated with the resting left ventricular ejection fraction (LVEF) measured by radionuclide ventriculography obtained within 14 days of the event. The mortality was highest in patients with an LVEF < 30% (9.9%). Patients not undergoing study for any reason had an intermediate mortality of 6.6%. (Data from Zaret BL, Wackers FJ, Terrin ML, et al: Value of radionuclide rest and exercise left ventricular ejection fraction in assessing survival of patients after thrombolytic therapy for acute myocardial infarction: Results of Thrombolysis in Myocardial Infarction (TIMI) phase II study. The TIMI Study Group. J Am Coll Cardiol 1995;26:73).

Nonsustained Ventricular Tachycardia

Another risk factor for SCD that was used as a screening tool in some primary prevention trials was the presence of nonsustained ventricular tachycardia (NSVT).[16] After the first 24 hours post-infarction, NSVT is detected in approximately 5% to 10% of the patients, particularly during the first months, and has been considered to have adverse prognostic significance. Data from many sources, including the Multicenter Postinfarction Research Group, showed that NSVT detected on 24-hour ambulatory monitoring at 1 week or later post-MI carried at least a twofold increased risk of SCD.[17] The patients at greatest risk are those with diminished left ventricular systolic function, with NSVT appearing to have little prognostic significance if ejection fraction is preserved. Moreover, it seems that in the β-blocking era, all common arrhythmia risk variables, including NSVT, may have diminished predictive power in identifying post-infarction patients at risk of SCD. The incidence and prognostic significance of NSVT have also been shown to be diminished in patients who have undergone thrombolysis.[18] In addition, NSVT on Holter monitoring may have low reproducibility (50% overall in one study), especially in patients with infrequent NSVT episodes.[19]

In the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT I), the role of an implantable cardioverter-defibrillator (ICD) was evaluated in patients with an earlier MI, and NSVT was used as one of the entry criteria. NSVT alone, however, was not considered sufficient to justify randomization in these studies; both required the additional criteria of LV dysfunction and inducible VT on EPS. In addition, patients were not enrolled sooner than 1 month in the MUSTT and 3 weeks in the MADIT I studies from their most recent MI.

Inducible VT/VF

Rates of inducibility of VT/VF at EPS differ based on the underlying substrate,[20] with inducibility rates being highest in the setting of coronary artery disease, especially in patients who have an underlying myocardial infarct/scar and in those who present with sustained monomorphic VT (SMVT; inducibility rates in the latter group exceed 90%). Inducibility rates are decreased in patients without coronary artery disease in those who present with cardiac arrest and those who present with nonsustained VT. The incidence of any inducible ventricular arrhythmia in cardiac arrest survivors varies in the literature from 46% to 85%. Only 37% of patients with nonsustained VT have inducible SMVT and 14% have sustained polymorphic VT/VF. Overall, the induction of SMVT at EPS in patients with an earlier myocardial infarction and NSVT is best predicted by the degree of LV dysfunction and the presence of regional wall abnormalities. A reduced rate of VT inducibility has been noted in patients with patent (as opposed to occluded) infarct-related arteries, despite comparable ventricular function between the two groups.[21] Induction of arrhythmia is less common in patients treated with a thrombolytic agent (15% to 20%).

In patients with no presenting arrhythmia, the prognostic value of EPS is controversial, although some studies suggest that the induction of sustained VT or VF in post-MI patients has strong predictive value for subsequent life-threatening arrhythmias.[22,23] In these studies, the induction of SMVT was strongly related to the degree of left ventricular dysfunction. The sensitivity of EPS in the post-MI setting is approximately 58% (specificity of 95%, positive predictive accuracy of 30% and a negative predictive accuracy of 98%). Despite the high negative predictive accuracy that was demonstrated in earlier studies, data from subsequent randomized trials (e.g., MUSTT) show that event rates are still substantial in patients who are noninducible; the high negative predictive accuracy of EPS noted in some studies is, therefore, believed to be related to the low incidence of events in this population versus the discriminant value of the test. In those patients who are inducible, SMVT is more specific than VF for predicting arrhythmic events and allows for the accurate identification of patients who may profit by prophylactic antiarrhythmic therapy.[24]

If one summarizes the results of multiple studies, approximately one third of post-MI patients had an arrhythmia induced during EPS; 18% of these patients (range 6% to 41%) had an arrhythmic event during a 1-year follow-up period. In contrast, the incidence of an arrhythmic event was only 7% (range 0% to 14%) in noninducible patients.

The predictive difference between patients with inducible and noninducible arrhythmias in the reperfusion era was evaluated in a registry of the MUSTT trial; all patients had an LVEF < 40% and NSVT. Patients who had inducible SMVT or VF and were untreated had significant increases in the rate of arrhythmic death or resuscitated SCD at 2 years (18% versus 12%) and five years (32% versus 24%) compared with those who did not have inducible SMVT or VF (Fig. 21–3).

Inducible sustained VT was used as an entry criterion, together with LV dysfunction and NSVT on ambulatory monitoring, in both the MUSTT and MADIT I trials of ICD therapy. The relatively high mortality rate in the noninducible patients in the registry of the MUSTT trial was one of the rationales for requiring only a low LVEF for inclusion in MADIT II. Although EPS was not a requirement for the MADIT II trial, such studies were performed in 593 of the 742 ICD-treated patients. The likelihood of inducibility was higher in patients with subsequent VT than in those who did not experience a device discharge (44% versus 34%) but was lower than in patients with subsequent VF.[25] When VT or VF, whichever occurred first, was used as a combined endpoint, inducibility was not useful in identifying which patients would receive appropriate ICD therapy for malignant ventricular arrhythmias. Overall, EPS was believed to be insufficient as a risk stratifier for malignant ventricular arrhythmias in patients who fulfilled the MADIT II criteria.

Rates of inducibility of monomorphic VT at EPS are significantly lower in the setting of dilated cardiomyopathy as compared with coronary artery disease, even though polymorphic ventricular arrhythmias can be induced in up to 86% of these patients.[26] More importantly, inducible ventricular arrhythmias are believed to be less predictive of arrhythmia recurrence and sudden death in the setting of NIDCM than in the setting of patients with IRCM. Because EPS has repeatedly been shown to have limited value, as it does in the risk stratification of patients with NIDCM, it has not been included as an entry criterion in any major ICD trial involving these patients.

Additional Noninvasive Risk Stratification for Sudden Cardiac Death

In addition to the risk factors already mentioned, other markers of malignant arrhythmias have been investigated to predict the risk of sudden cardiac death in patients after MI and in patients with nonischemic cardiomyopathy. The sensitivity and specificity of any single test for predicting major arrhythmic events are limited. This was illustrated in a pooled analysis of 44 studies of over 25,500 patients where the sensitivity and specificity of individual tests ranged from 43% to 62% and 77% to 86%, respectively.[27] Despite the limited predictive accuracy of any single clinical variable or test in better predicting arrhythmic outcomes, the use of a combination of clinical variables and/or tests has been shown to significantly increase the ability to predict the rates of total, as well as arrhythmic, mortality in a given population. For example, although the predictive value of heart rate variability (HRV) for post-infarction risk stratification is independent of other factors such as depressed LVEF, increased ventricular ectopic activity, and the presence of late potentials, decreased HRV by itself is insufficient as a single risk stratifier. HRV has a low overall predictive value for the rate of total or sudden-death mortality, but the value increases to almost 50% when HRV is combined with traditional risk factors such as VPCs, signal-averaged ECG (SAECG), or LVEF. A variety of studies have also evaluated the usefulness of other noninvasive markers (alone or in combination with each other) such as SAECG , baroreflex sensitivity (BRS), T wave alternans (TWA), and QRS prolongation on ECG (Table 21–2).[56-58]

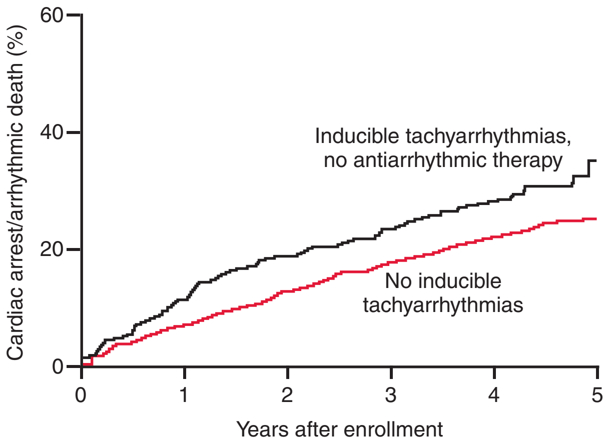

Figure 21–3 Induction of ventricular arrhythmia identifies a high-risk patient. In the MUSTT trial, the outcome of 353 patients with coronary disease, a left ventricular ejection fraction ≤40%, and a sustained ventricular tachyarrhythmia induced during electrophysiologic study—but who did not receive antiarrhythmic therapy—was compared with those of 1397 patients without an inducible ventricular tachyarrhythmia who were entered into a registry. Kaplan-Meier analysis showed that the rate of cardiac arrest or arrhythmic death was lower in patients without inducible arrhythmia at 2 (12% versus 18% for those with inducible arrhythmia) and 5 years (24% versus 32%, adjusted $P <$ 0.001). Overall mortality at 5 years was significantly lower in those without inducible arrhythmia (44% versus 48%). (Data from Buxton, AE, Lee, KL, DiCarlo, L, et al: Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial investigators. N Engl J Med 2000;342:1937.)

Trials of Primary Prevention

Risk stratification for fatal arrhythmias after acute MI has become more important because it is used to guide the selection of patients who will benefit from an ICD. The role of the risk stratification variables mentioned earlier in selecting patients for such therapy has been explored in several major randomized trials. These trials include patients with a reduced LVEF after MI (MUSTT, MADIT I, and MADIT II; Table 21–3),[1,15,28,29] patients with a reduced LVEF undergoing a revascularization procedure (Coronary Artery Bypass Graft [CABG]-Patch and Defibrillator in Acute Myocardial Infarction Trial [DINAMIT]; Table 21–4),[30,31] and patients with a reduced LVEF and NIDCM (The Cardiomyopathy Trial [CAT], Amiodarone Versus Implantable Cardioverter-Defibrillator [AMIOVERT], Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation [DEFINITE], and the

Table 21–2 Noninvasive Risk Factors for Sudden Cardiac Death*

Noninvasive Risk Factor	Comment
QRS prolongation on ECG	Intraventricular conduction delay and LBBB have been associated with a 50% increase in arrhythmic and total mortality
Late potentials on Signal-Average ECG (SAECG)	Defined as a filtered QRS duration >114 msec, a terminal (last 40 msec) QRS root mean square voltage <40 μV, and a low amplitude (<40μV) late potential duration >38 msec; late potentials have a negative predictive accuracy of 95-99% for VT in post-MI patients with a single risk factor (e.g., ventricular ectopy or severe LV dysfunction), but a positive-predictive accuracy of only 14-29%.[43,44]
Heart Rate Variability (HRV) and Baroreflex Sensitivity (BRS)[45]	Relative risk of cardiac mortality was increased by low values of either HRV or BRS in the ATRAMI trial, particularly when associated with an LVEF < 35%. As noted in the DINAMIT trial, reduced HRV may identify patients at high risk, not only for arrhythmic death, but also for nonarrhythmic death.
T Wave Alternans (TWA)[46]	High sensitivity and specificity for predicting inducible ventricular arrhythmias on EPS

*Data from references 15, 29, 31, 56-58.
ECG, electrocardiogram; EPS, electrophysiology study; LBBB, left bundle branch block.

Table 21–3 Primary Prevention Trials: Post Myocardial Infarction

Trial	Purpose	Patients	Mean LVEF, and NYHA Class	Primary Endpoint; Follow-Up (years)	All-Cause Mortality in ICD vs. Non-ICD Group; Relative Risk Reduction; Number Needed to Treat (NNT)	SCD Mortality in ICD vs. Non-ICD Group; Relative Risk Reduction; Number Needed to Treat (NNT)	Annualized All-Cause Mortality in ICD vs. Non-ICD Group (Reported Number/Mean Follow-Up)	Annualized SCD Mortality in ICD vs. Non-ICD Group (Reported Number/ Mean Follow-Up)
MADIT I (Moss et al. N Engl J Med 1996;335: 1933)	Compare ICD with med Rx in post-MI, low LVEF patients	196 patients with MI > 3 weeks prior, LVEF ≤ 35%, sustained monomorphic VT or VF unresponsive to procainamide	26%; I: 35% II-III: 65%	All-cause mortality; 2.25 mean	16% vs. 39% at 5 years; RR = 54%; NNT = 4	3% vs. 13% over 5 years; RR = 77%; NNT = 10	7% vs. 17%	1% vs. 6%
MUSTT (Buxton et al. N Engl J Med 1999; 341:1882	Compare antiarrhythmic therapy guided by EPS with standard care in post-MI patients with reduced LVEF and NSVT	704 with MI > 4 days prior, NSVT, LVEF ≤ 40%, inducible sustained monomorphic VT or VF at EPS	30%; I: 37% II: 39% III: 24%	Cardiac arrest or death from arrhythmia; 3.3 median	24% ICD vs. 55% (AAD) at 5 years; RR = 56% NNT = 4	9% ICD vs. 37% (AAD) over 5 years; RR = 76; NNT = 4	7% vs. 17%	3% vs. 11%
MADIT II (Moss et al. N Engl J Med 2002; 346: 877)	Evaluate the survival benefit ICD in patients with a prior MI and LVEF ≤ 0.30	1232 with MI > 4 weeks prior and PCI/CABG > 3 months prior	23%; I: 37% II: 35% III: 24%	All-cause mortality; 1.8 mean	14% vs. 20% at 1.8 years; RR = 31%; NNT = 17	(not reported)	8% vs. 11%	(not reported)

EPS, Electrophysiology study; ICD, Implantable cardioverter-defibrillator; LVEF, Left ventricular ejection fraction; MI, myocardial infarction; NNT, number needed to treat; NSVT, nonsustained ventricular tachycardia; PCI/CABG, percutaneous coronary intervention/coronary artery bypass graft; VF, ventricular fibrillation, VT, ventricular tachycardia.

Table 21–4 Primary Prevention Trials: Post-Revascularization Procedure

Trial	Purpose	Patients	Mean LVEF, and NYHA Class	Primary Endpoint; Follow-Up (years)	All-Cause Mortality in ICD vs. Non-ICD Group; Relative Risk Reduction; Number Needed to Treat (NNT)	SCD Mortality in ICD vs. Non-ICD Group; Relative Risk Reduction; Number Needed to Treat (NNT)	Annualized All-Cause Mortality in ICD vs. Non-ICD Group (Reported Number/Mean Follow-Up)	Annualized SCD Mortality in ICD vs. Non-ICD Group (Reported Number/ Mean Follow-Up)
CABG-Patch (Bigger et al., N Engl J Med 1997; 337: 1569	Evaluate survival benefit of ICD at the time of CABG in patient with LVEF ⩽ 35% and abnormal SAECG	900 with LVEF ⩽ 35% and abnormal SAECG getting elective CABG	27%; II or III: 73%	All-cause mortality; 2.7 mean	23% vs. 21% over 2.7 years (NS)	16% vs. 16% (cardiac deaths; NS)	9% vs. 8%	6% vs. 6%
DINAMIT (Hohnloser et al., N Engl J Med 2004; 351:2481	Evaluate survival benefit of ICD within 6-40 days after MI	674 with MI within 6-40 days, LVEF ⩽ 35%, abnormal heart rate variability	28%; I: 13% II: 61% III: 28%	All-causes mortality; 2.5 mean	19% vs. 17% at 2.5 years (NS)	4% vs. 8% at 2.5 years; RR = 0.58; NNT = 20	8% vs. 7%	2% vs 3%

Comparison of ICD and non-ICD use in trials of primary prevention in patients undergoing coronary revascularization procedures.[30,31] Annualized figures represent the reported endpoint in each group divided by the average follow-up period. AAD, antiarrhythmic drug; CABG, coronary artery bypass graft; EPS, electrophysiology study; ICD, implanted cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NNT, number needed to treat, NS, nonstatistically significant; NSVT, nonsustained ventricular tachycardia, PCI, percutaneous coronary intervention; RR, relative risk reduction; SAECG, signal-averaged electrocardiogram; VF, ventricular fibrillation.

Table 21–5 Primary Prevention Trials: Non-ischemic Cardiomyopathy

Trial	Purpose	Patients	Mean LVEF, and NYHA Class	Primary Endpoint; Follow-Up (years)	All-Cause Mortality in ICD vs. Non-ICD Group; Relative Risk Reduction; Number Needed to Treat (NNT)	SCD Mortality in ICD vs. Non-ICD Group; Relative Risk Reduction; Number Needed to Treat (NNT)	Annualized All-Cause Mortality in ICD vs. Non-ICD Group (Reported Number/Mean Follow-Up)	Annualized SCD Mortality in ICD vs. Non-ICD Group (Reported Number/Mean Follow-Up)
CAT (Bansch et al., Circulation 2002 105:1453)	Evaluate survival benefit of ICD in NIDCM and LVEF $\leqslant$ 30%	104 with NIDCM $\leqslant$ 9 months and LVEF $\leqslant$ 30%	24%; I: 0% II: 65% III: 35%	All-cause mortality; 5.5 mean	27% vs. 32% at 6 years (NS)	(not reported)	5% vs. 6%	(not reported)
AMIOVERT (Strickberger et al., J Am Coll Cardiol.2003; 41:1707	Compare ICD with amiodarone in patients with NIDCM and NSVT	103 with NIDCM, NSVT, and LVEF $\leqslant$ 35%	23% I: 15% II: 64% III: 20%	All-cause mortality; 2 mean	12% vs. 13% at 2 years (NS)	2% vs. 4% at 2 years (NS)	6% vs. 7%	1% vs.2%
DEFINITE (Kadish et al., N Engl J Med 2004;350: 2151)	Evaluate survival benefit of ICD in patients with NIDCM and LVEF < 35%	458 with NIDCM, LVEF $\leqslant$ 35%, and PVCs or NSVT	21%; I: 22% II: 57% III: 21%	All-cause mortality; 2.4 mean	8% vs. 14% at 2 years; RR = 0.35 (p = 0.08)	1% vs. 6% over trial duration; RR = 0.80; NNT = 20	3% vs. 6%	0.4% vs. 3%
SCD-HeFT (Bardy et al., N Engl J Med 2005;352:225	Compare ICD with amiodarone in patients with CHF and LVEF $\leqslant$ 35%	2521 with NYHA II-III CHF and LVEF $\leqslant$ 35%	25%; I: 0% II: 70% III: 30%	All-cause mortality; 3.8 (median)	22% vs. 28% (amiodarone) at 5 years; RR = 23%; NNT = 13	(not reported)	4.4% vs. 5.7%	(not reported)

Comparison of ICD and non-ICD use in trials of primary prevention in patients with non-ischemic dilated cardiomyopathy (NIDCM).[32-35] Annualized figures represent the reported endpoint in each group divided by the average follow-up period. The SCD-HeFT trial included patients with infarct-related cardiomyopathy as well as NIDCM. AAD, antiarrhythmic drug; CABG, coronary artery bypass graft; EPS, electrophysiology study; ICD, implanted cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NNT, number needed to treat; NS, nonstatistically significant; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVC, premature ventricular contraction; RR, relative risk reduction; VF, ventricular fibrillation.

Sudden Cardiac Death-Heart Failure Trial [SCD-HeFT; Table 21–5).[32-35]

PRIMARY PREVENTION OF SUDDEN DEATH IN OTHER DISEASES

A number of diseases other than IRCM and NIDCM have been associated with an increased incidence of sudden cardiac death. These include inherited diseases of ion channels, such as long-QT syndrome, Brugada syndrome, and catecholaminergic VT. Other structural heart diseases, such as right ventricular dysplasia, hypertrophic cardiomyopathy, and certain types of congenital heart disease, may also be associated with an increased risk of sudden death. The incidence of these conditions is far less than those of IRCM and NIDCM—making prospective, randomized, control trials difficult to perform. Nonetheless, nonrandomized observational studies suggest that subgroups of high-risk patients may benefit from ICD therapy.

Hypertrophic Cardiomyopathy

Ventricular ectopic beats and episodes of NSVT are common in patients with hypertrophic cardiomyopathy (HCM). In addition, the annual incidence of SCD is increased to 1% to 4% in patients with HCM. Myocardial scarring and fibrosis is believed to contribute significantly to the arrhythmic phenotype in this condition. NSVT appears to confer increased risk for SCD, and certain high-risk patients with NSVT may be candidates for a defibrillator (e.g., those with episodes of NSVT that are prolonged, repetitive, or associated with symptoms of impaired consciousness). Other risk factors for sudden death include survival from cardiac arrest, spontaneous sustained VT, a family history of HCM-related premature SCD, marked hypertrophy with a left ventricular thickness ≥30 mm, and an attenuated or hypotensive blood pressure response to exercise.

Congenital Long QT Syndromes

Mutations in seven genes have been identified in patients with genetic long QT syndrome (LQTS) (see Chapter 25). The vast majority of cases of LQTS are accounted for by three of the seven genotypes: LQT1 (40% to 55%), LQT2 (35% to 45%), and LQT3 (8% to 10%). The incidence of congenital LQTS in the United States is estimated to be 1 in 7000 to 10,000; the condition causes 3000 to 4000 deaths in children annually. The syndrome is associated with an increased risk of polymorphic VT (torsades de pointes) with presenting symptoms that include palpitations, syncope, seizures, and cardiac arrest. Arrhythmia triggers vary with the underlying genotype but typically include exercise for LQT1, acute arousal events (such as exercise, emotion, or noise) for LQT1 and LQT2, and rest or sleep for LQT3. Symptomatic untreated patients with LQTS are at high risk of SCD, with mortality rates of up to 20% at 1 year and 50% to 60% at 10 years. Although β-blockers are the mainstay of therapy for congenital LQTS, ICD implantation is being recommended for survivors of cardiac arrest and for patients with persistent torsades de pointes despite conventional therapy.

Brugada Syndrome

Brugada syndrome is associated with a peculiar pattern on the electrocardiogram (ECG) that consists of a pseudo-right bundle branch block (RBBB) and persistent ST-segment elevation in leads V_1 to V_3 (see Chapter 25). The condition is significant for its propensity for malignant ventricular arrhythmias. SCD may be the first and only clinical event in Brugada syndrome, occurring in as many as one third of patients. Arrhythmic events generally occur between ages 22 and 65 and are more common at night than during the day and during sleep versus while awake. Male sex and a positive family history of SCD are considered risk factors for SCD. Importantly, patients with a previous history of SCD and those with a history of syncope are at significantly increased risk for subsequent arrhythmic events as compared with asymptomatic individuals. Current guidelines advocate ICD implantation for patients with a history of aborted SCD or sustained VT, with the evidence being less well established in patients who have either syncope or a family history of unexplained sudden death. The role of EP testing is uncertain at this time, although a recent study revealed a significant predictive value for EPS in a large series of patients with Brugada type 1 ECG pattern.[36] A randomized trial was performed recently in Thailand in patients with an inherited risk of SCD (sudden unexpected death syndrome, which is believed to represent Brugada syndrome); in this trial (DEBUT)[37] patients were found to have improved survival with an ICD versus β-blocker therapy.

COST EFFECTIVENESS OF THE ICD

The increased ICD use that has resulted from the aforementioned clinical trials has potentially created an enormous financial burden on the health care economy. At this time, there are more than three million patients in North America who are eligible for an ICD based on MADIT II criteria; approximately 400,000 new patients are expected to be added to their ranks each year. A defibrillator costs approximately $30,000 per patient. This translates into an initial cost of $90 billion, with annual costs thereafter being estimated at $12 billion a year—staggering sums by any estimate!

Attempts have also been made to perform cost-effectiveness analysis for ICD use, with analyses, to date, ranging from $20,000 to $70,200 per life-year gained[38,39] (see Chapter 1). Because a treatment is generally considered to be cost effective if its cost is similar to that of hemodialysis—between $35,000 and $60,000 per life-year gained—ICDs compare relatively favorably. Unfortunately, this does not lessen their financial impact on an already strained health care budget.

The hope is that ICDs will become less expensive over time, as research and development costs are gradually recovered by industry; market competition will also likely play a role. There is also pressure on ICD manufacturers to develop inexpensive shock-only devices in order to drive down ICD cost. Other than attempts to curtail the cost of these devices, a "fine-tuning" of ICD use in patients who are most likely to use them will also decrease the cost of ICD therapy. Attempts at better risk stratification for SCD (and resulting ICD use) are ongoing.

COMPLICATIONS, FOLLOW-UP, AND SPECIAL CONSIDERATIONS

Although the implantation of ICDs continues to become easier—both in terms of smaller systems and improved equipment—complications still occur. Device infection can occur in up to 1% to 2% of cases and may require extended antibiotic use or repeat procedures.[40] Lead malfunction may cause delivery of inappropriate shocks and changes in the patient's metabolic condition due to the addition of medication or from electrolyte abnormalities that may increase the defibrillation threshold (see Appendix 2). The psychological stress of frequent ICD shocks, appropriate or inappropriate, may also negatively impact a patient's quality of life (Table 21–6).

After ICD implantation, routine follow-up is mandatory. This usually includes a wound check within the first few days to weeks after implantation, as well as scheduled visits to monitor lead and device functioning and documentation of bradycardia and tachycardia therapies. Unnecessary pacing has been shown to have adverse effects and should be assessed.[41,42] An important aspect in care of the patient with an ICD is to provide recommendations about how to respond to a device discharge (Fig. 21–4).[43] Because the application of a magnet over an ICD will suspend ICD tachycardia therapies (i.e., device discharge) but will not affect bradycardia therapies, special consideration must be made for patients undergoing surgery. In pacemaker-dependent patients with an ICD, reprogramming may be necessary to ensure an adequate heart rate during surgery because electrocautery may inappropriately inhibit function (Fig. 21–5).[44]

CURRENT GUIDELINES FOR ICD THERAPY

The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS; formerly known as the North American Society of Pacing and Electrophysiology, NASPE) updated guidelines for ICD implantation in 2002, and the European Society of Cardiology (ESC) published its guidelines in 2003.[45-47] Based on these guidelines and incorporating the results of randomized studies published since their publication, the Center for Medicare & Medicaid Services (CMS) expanded the indications for coverage for ICD insertion in January 2005.[48] An algorithm for the indications for ICD implantation is presented in Figure 21–6.

FUTURE DIRECTIONS

Novel factors are being sought to stratify patients at risk of SCD more effectively. The search for better markers of ventricular arrhythmias is being driven by the observation that

Table 21–6 Complications of ICD Therapy

Device-Related	Therapy-Related
• Infection or erosion	• Inappropriate shocks
• Hematoma	• Acceleration of VT
• Pneumothorax	• Psychological trauma (frequent shocks)
• Lead dislodgment	• Unintended hospitalization
• Inadequate defibrillation threshold	
• Lead malfunction	
• Electromagnetic interference	

Complications of implanted cardioverter defibrillator therapy.
(From DiMarco JP: Implantable cardioverter-defibrillators. N Engl J Med 2003;349:1836-7.)

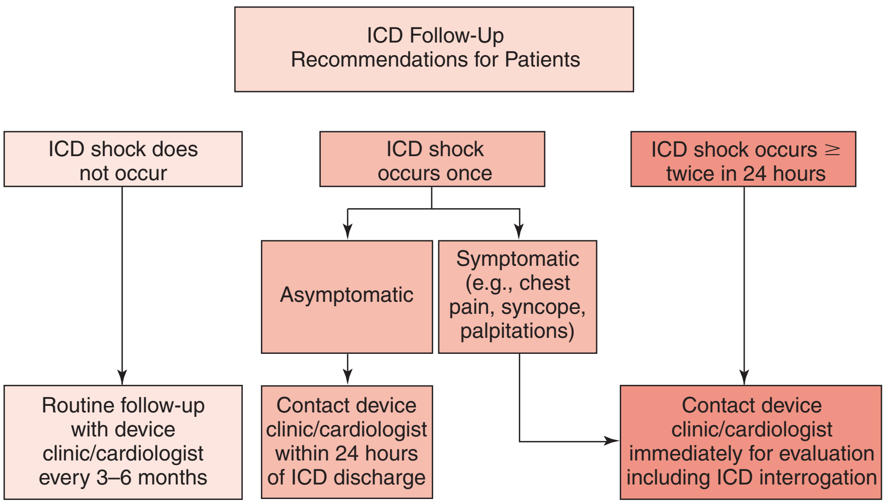

Figure 21–4 ICD follow-up recommendations for patients. If no device discharge occurs, then follow-up should be routine. If a single shock occurs and the patient is asymptomatic, then the device clinic/cardiologist should be contacted within 24 hours. If the patient is symptomatic or has more than one shock within 24 hours, the patient should immediately contact the device clinic/cardiologist; in some cases, the management will be done as an outpatient. ICD, implantable cardioverter-defibrillator. (From Sears SF, Jr., Shea JB, Conti JB: Cardiology patient page: How to respond to an implantable cardioverter-defibrillator shock. Circulation 2005;111:e380-2.)

the majority of SCD occurs in patients who would not be considered "high risk" by any of the currently available risk-stratification methods and by the cost of ICD implantation and use. More sensitive tests are needed to identify patients in what are now considered low-risk populations (e.g., those with coronary artery disease but no prior history of sudden cardiac death and preserved left ventricular systolic function). Furthermore, as indications for ICD use broaden, the sheer expense of ICD therapy threatens to make widespread implantation prohibitive in most countries. Although some have suggested a need to manufacture cheaper devices (i.e., ICDs that can deliver appropriate therapy for ventricular tachyarrhythmias but lack several of the currently available diagnostic features),[49] many others feel that better risk stratification may be the key to keeping costs down. Of the available tests, LVEF is still the most sensitive but suffers from a lack of specificity. Only approximately 23% of MADIT II patients actually receive appropriate therapy from their devices for potentially life-threatening ventricular arrhythmias (at an average follow-up of 21 months). The role of an ICD in all patients meeting MADIT II criteria is, therefore, controversial. Some have suggested that the benefit of ICD therapy in MADIT II patients might be largely limited to patients with inducible VT, which was an entry criterion in MADIT I and MUSTT. However, inducibility at EPS was not found to be sufficient as a risk stratifier in the MADIT II study population.

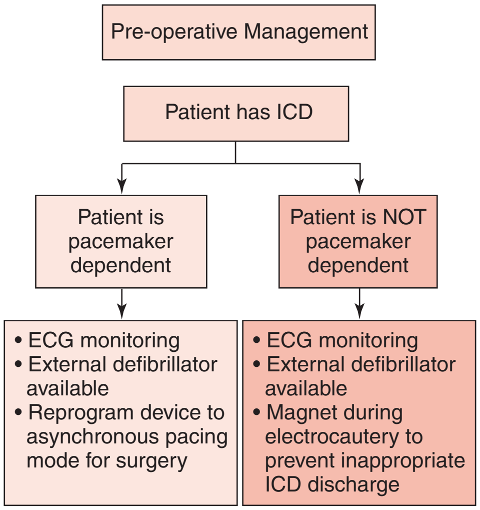

Figure 21–5 Suggested management of patients with ICDs at the time of surgery. Reprogramming may be necessary if the patient is pacemaker dependent because magnet placement will suspend tachycardia therapies but will not change bradycardia parameters and therapies. ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator. (From Blomberg P: Personal communication, 2005.)

Role of Cardiac Imaging in Risk Stratification for SCD

Two imaging modalities are currently being investigated: nuclear imaging to visualize the cardiac nervous system and cardiac MRI to assess for nonviable myocardium (and the resultant risk of malignant arrhythmias). Imaging of the cardiac autonomic nervous system has been performed by several groups with radiopharmaceutical agents such as

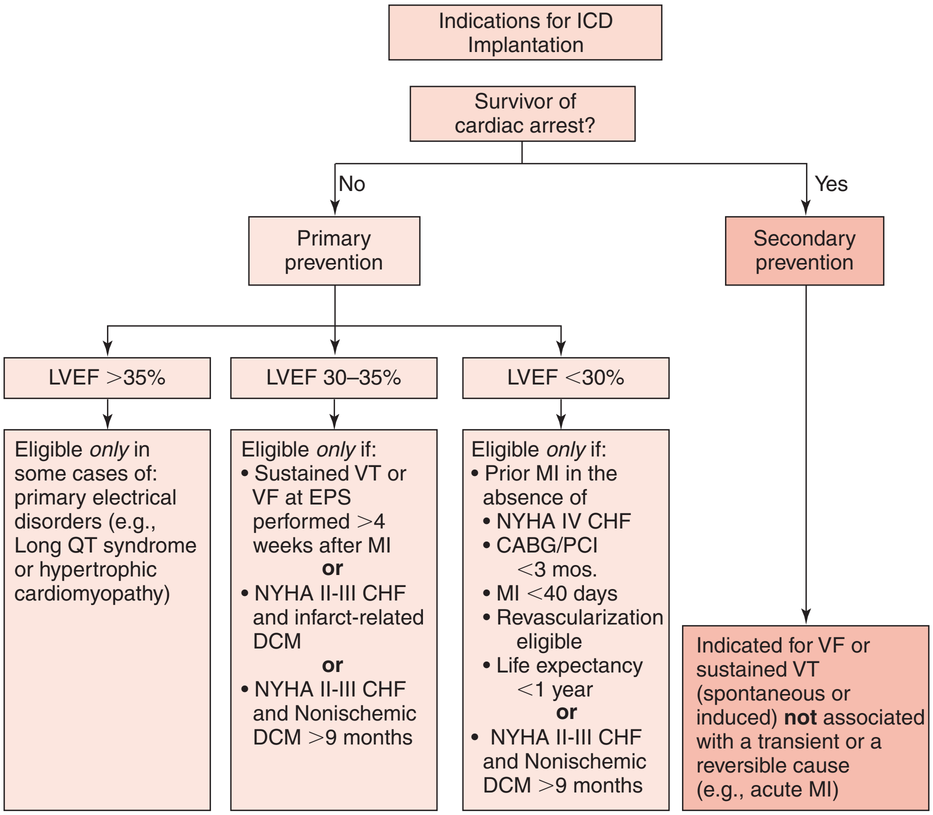

Figure 21–6 Algorithm for indications for ICD implantation. CABG/PCI, coronary artery bypass graft/percutaneous coronary intervention; CHF, congestive heart failure; DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia. (From references 45 to 48.)

^{123}I-MIBG (using a gamma camera) or ^{11}C-HED (using PET). The extent and heterogeneity of sympathetic denervation with either agent have been shown to be predictive of ventricular arrhythmias or SCD. A combination of ^{123}I-MIBG and HRV variables has been demonstrated to correlate with ICD shocks in a heterogeneous population of ICD patients.[50] An increase in the use of autonomic imaging of the heart, in conjunction with other markers of SCD, may thus enhance the ability to detect patients who may benefit most from ICD use.

Cardiac MRI also holds promise as a method of risk stratification for SCD. Studies[51,52] have demonstrated the sensitivity of cardiac MRI in detecting nonviable myocardium or scar, even when the global LVEF appears to be well preserved. Bello and colleagues[53] have shown a significant correlation between left ventricular scar as detected on cardiac MRI and inducible ventricular tachyarrhythmias at electrophysiologic study. In this study, infarct surface area and mass—as measured by cardiac MRI—were better identifiers of patients who have a substrate for monomorphic ventricular tachycardia rather than LVEF. As a result, an ICD trial being planned will assess the usefulness of MRI to better risk stratify patients with mild-to-moderate left ventricular dysfunction.

Role of Genetic Testing in Prediction of SCD

Basic, as well as clinical, studies performed over the last few years point toward intricate genetic mechanisms that underlie not just the genetics of ion channel function but also atherogenesis, plaque destabilization, and the thrombotic cascade.[54] Advances in molecular and genetic electrophysiology include an increased understanding of the genes that control ion channel pore structure (e.g., KvLQT-1, HERG, and SCN5A) and those that control their associated modulatory peptides (e.g., minK, MiRP-1). Genes that modulate or modify calcium handling (e.g., RyR2 and CASQ2) are associated with arrhythmias, some of which may occur because of interactions between these calcium handling proteins and the KvLQT-1/minK complex. Interactions between multiple genes, as well as interactions occurring between genetic and environmental factors, may be required for final common pathophysiologic pathways such as atherogenesis, the thrombotic cascade, and the resulting arrhythmic phenotype. Stepwise integration of these characteristics for individuals by means of complex analytic methods offers the hope of a field of genetic epidemiology that would more accurately identify those patients at increased risk of SCD.[55]

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Chapter 22

Surgical Options for the Treatment of Arrhythmias

Adam E. Saltman

CHAPTER CONTENTS

Overview of the History of Surgical Therapy for Arrhythmias

The surgical treatment of cardiac arrhythmias has undergone significant change over the last four decades. Although many of these procedures were among the first performed by the nascent field of cardiac surgery, they have undergone one of the most astounding cycles of development and then recession seen anywhere in medicine. The purpose of this chapter is to overview this history briefly and then to concentrate on those procedures in use today by the cardiac surgeon, how they are developing and changing rapidly, and how they will be applied in the near future.

Summary of the Field Today

Unlike all other operations performed by the cardiac surgeon, those designed to treat arrhythmias are, by nature, ablative: They destroy tissue in order to restore normal rhythm and electrical conduction. In the early days of cardiac surgery, when cardiopulmonary bypass was still a very dangerous adjunct, the subspecialty of cardiac electrophysiology did not yet exist. Hoffman and Cranefield[1] provided the basis of principles in the basic laboratory and the pioneering studies of Durrer and colleagues[2] led to the use of surgery to treat arrhythmias.

The job of the surgeon was first to understand the mechanism underlying the arrhythmia, and second, to destroy it. This might mean transecting an accessory bypass tract, locating and ablating a focus of abnormal automaticity, or even creating lines of conduction block in order to stop reentrant wavelets. Through these efforts much was learned about the anatomy of the heart, about epicardial and endocardial mapping, interpretation of electrograms, and about methods of tissue destruction that could safely remove abnormal tissue yet leave the heart a functioning syncytium. The progress over the last two decades has been one more of miniaturization than of discovery.

The task confronting today's surgeon is how to apply his or her skills in the manner that best complements those of colleagues in the electrophysiology laboratory. For some arrhythmias, there is no doubt that an endocardial percutaneous approach is best, yet for others this is not the case. The challenge for surgeons of today and tomorrow is to provide the best approach to the heart for specific arrhythmia treatment yet combine this with the least invasive methods and—most of all—maintain efficacy.

HISTORICAL PROCEDURES

Wolff-Parkinson-White Ablation

The existence of electrical conduction across the atrioventricular (AV) groove was first demonstrated in 1967 during intraoperative mapping.[3] The Duke group was the first to report the successful surgical treatment for Wolff-Parkinson-White (WPW) syndrome in 1968.[4] The procedure involved approaching the heart via a median sternotomy mapping the site of earliest ventricular activation during atrial pacing (ventricular insertion rate) and the earliest site of atrial activation during circus movement tachycardia. The AV ring was then incised to cut the accessory pathway.

As experience increased, cure could be attained in nearly 100% of patients. By the 1980s, hundreds of cases were being performed yearly. By the end of the 1980s, however, transvenous catheter ablation techniques were developed. Currently, catheter ablation techniques (see Chapter 20) have almost completely obviated the open surgical approach.[5] Nevertheless, there are patients in whom catheter-based ablation is occasionally unsuccessful and a surgical approach is still needed.

Atrioventricular Nodal Reentrant Tachycardia

Reentry within the AV node results from communication between the slow and fast pathways of conduction involving the AV node and transitional fibers[6] (see Chapter 23). Ross and colleagues developed a surgical approach to treat AV nodal reentry,[7] but this was replaced by catheter ablation.[8,9] Surgical ablation of the AV node had been performed for many years until Dr. Scheinman introduced transcatheter ablation in 1982, using high-energy shocks within the His bundle region.[10] Currently, ablation of the AV node with RF energy is the preferred method.

Post-infarction Ventricular Tachycardia

Ischemic ventricular tachycardia after myocardial infarction remains a significant problem, especially as survival continues to improve after myocardial infarction. It has generally been thought that these arrhythmias resulted from reentry in heterogeneous tissues surviving after infarction. Endocardial and epicardial catheter mapping of VT was pioneered by Josephson and colleagues.[11,12] This led to map-guided subendocardial resection to treat VT.[12,13]

Endocardial resection and ablation, combined with repair of ventricular aneurysms, has become a highly effective treatment for this disorder.[14,15] Considering the patient population on whom this operation is performed, however, there has been a significant degree of morbidity and mortality. Combined with advances in catheter ablation techniques and the demonstration of the effectiveness of implantable cardioverter-defibrillators, this procedure has also been almost completely eliminated from surgical practice, confined only to those patients who have incessant tachycardias and have been refractory to drug therapy, had complications from catheter therapy, or who also are to be treated for advanced-stage heart failure or complications from their large ventricular aneurysms. This is unfortunate because, unlike ICDs, surgery cures the problem. There may be a resurrection of surgery in the future.

CURRENTLY PERFORMED PROCEDURES

Atrial fibrillation

Atrial fibrillation, far from being a nuisance arrhythmia, has been clearly shown to increase mortality and to inflict considerable morbidity on its victims. Despite four decades of attempts at pharmacologic therapy, little success has been achieved, and many of the drugs in use today carry with them significant, limiting side effects. Over the last 10 years, there has been an explosion in the level of interest in nonpharmacologic treatments for atrial fibrillation (AF) (Figs. 22–1 to 22–3).

The Electrophysiologic Basis of Atrial Fibrillation and the Development of a Procedure

The initial attempts at the surgical treatment for AF focused mainly on "disconnecting" the atria from the ventricles, mainly to control ventricular response. The right atrial isolation operation,[16] the left atrial disconnection operation,[17] and the Corridor operation[18,19] all met with reasonably high success rates. However, those procedures left components of the atria still fibrillating. The patient remained exposed to the risk of stroke and required continuing therapy with anticoagulants and their attendant risks. In effect, they were no better at treatment than the commonly performed percutaneous AV nodal ablation procedure, yet the latter therapy avoided open heart surgery.

The theoretical principles underlying AF were proposed 100 years ago. Experimental evidence in the past four decades suggested that reentry could serve as the mechanism for AF. It was not until Dr. Cox and Boineau's pioneering work in the 1980s that proof was obtained in vivo. They were able to show in human and animal mapping experiments using high-density multipolar electrodes that AF was a self-sustaining arrhythmia, dependent on multiple reentrant waves wandering at random throughout the atrial syncytium.[20,21] Despite making considerable steps toward the development of such a procedure, which included transecting the posterior atrium, isolating the pulmonary veins (PVs), and creating linear lesions toward the mitral annulus and the inter-atrial septum, the operation would not stop AF reliably in humans.[22]

As further experience was gained in the laboratory and the operating room, it became apparent that AF might not be the result of a single underlying mechanism but rather a combination of several possible mechanisms. Unfortunately, it remains technically impossible to complete the construction and analysis of a complete activation map of atrial fibrillation in real time. Thus, an anatomically guided operation was designed to treat as many patients as possible. The resulting iterations of Dr. Cox's Maze procedure, now settling on the Maze-III, have become the standard approach for patients undergoing surgery for AF. This operation has met with a very high degree of success over long-term follow-up (see later) and is today the standard against which other procedures must be compared. It has been the interest of many surgeons since the mid-1990s to adapt the Maze-III to a less invasive and less morbid approach.

Subsequent work has been done in advancing real-time intraoperative mapping and in tailoring surgical therapy either toward the PVs or the entire atrium, depending on the individual patient's arrhythmia. However, there has currently been no validation of mapping during AF as a useful guide to surgical therapy. We will have to wait to see if this approach evolves to be an accurate, reproducible, and meaningful method of guiding surgery.

The Experience with the Maze Operation

In its current incarnation, the Maze-III operation has met with excellent success in a wide variety of settings and institutions. Gratifyingly, the mortality rate of the operation has been low, ranging from 1.4% to 3.6%.[23-25] When performed for lone AF, it has been reported to "cure" as many as 96.3% of patients.[23] When applied during mitral valve surgery, it restores sinus rhythm in 65% to 82% of patients.[24,25] It has been used with reoperations as well as with coronary bypass grafting and aortic valve replacements.[25-27]

One of the most interesting findings in patients who have undergone the Maze-III procedure is that there is a reportedly low incidence of stroke, less than 0.1% per year in Dr. Cox's experience.[28,29] This is surprising because these patients carry a large burden of suture and pledget material in their atria and are not typically placed on anticoagulant therapy. Possibly this is because the left atrial appendage has been removed from each patient, but it may also be a result of restored right and left atrial transport function in the majority of patients, although the extent of that restoration is controversial.[30-32]

The Design of an Effective Ablative Procedure

It has been only over the last 10 years that scientific data have become available concerning the underlying pathophysiologic mechanisms of AF. This is largely because of the appearance

of an animal model of permanent AF,[33] as well as the demonstration in humans that episodes of paroxysmal AF may begin in or around the PVs.[34]

With regard to paroxysmal AF, these findings have led to a tremendous surge in interest toward either ablating PV foci or electrically disconnecting the PVs from the remainder of the left atrium. As a result of its original design, the Maze procedure mandated creating a completely encircling line of scar around all four PVs as a single pedicle. It would have been expected to eliminate—and has been quite successful at eliminating—paroxysmal AF. Attempts to recreate the Maze lesion set with endocardial RF probes met with very long and sometimes multiple EP laboratory sessions, low success rates, and high complication rates.

The developments in catheter ablation have mirrored what has been known to the surgeon for some time: A complete electrical disconnection of the PV *pedicle* or *antrum,* possibly requiring the portion of the left atrial wall posteriorly and between the PVs results in a high "cure" rate for patients with paroxysmal AF (see Fig. 22–1). This remains the cornerstone of treatment for these patients because, even though several investigators have now shown that abnormal impulses can originate outside of this region,[35,36] the majority of patients with PAF can be treated by this encompassing ablative approach.

With regard to permanent fibrillation, however, the situation is far more complex. Some investigators have shown that the mechanism underlying permanent fibrillation is possibly random reentry[37]; others suggest that focal drivers or "mother rotors" may perpetuate the arrhythmia.[38,39] In view of this uncertainty, it is unlikely that isolation of one or even a small number of atrial muscle regions or veins will prove successful at treating these patients. Rather, it will more likely be necessary to create conduction obstacles that prevent reentry by containing excitation to defined regions of the atrium, extinguishing abnormal impulses yet preserving connections among regions and between the SA node and the AV node. The design of the Maze procedure(s) has attempted to achieve this and, as discussed earlier, has met with excellent success and durability.

It is, therefore, rational to employ different ablative strategies for patients presenting with different forms of AF. Rather than mapping the location of each site of impulse origination in each patient with paroxysmal AF, it would be more effective to electrically isolate the PVs and posterior left atrial wall from the rest of the atrium. This would be expected to successfully treat approximately 90% of PAF originating in pulmonary veins. For patients presenting with or progressing to more permanent forms of AF, however, a more complete lesion set would be advised: This set should isolate the PVs but also include extensions to the mitral annulus, the left atrial appendage, and even over the right atrium (see Fig. 22–3) until it has been proved that these Maze lesions are not necessary. This argument is made stronger if lesion creation can be accomplished with little or no additional risk to the patient.

It is with this in mind that future procedures must be designed, implemented, and studied. The random application of poorly defined lesion sets to heterogeneous groups of patients just because "they have AF" should be discouraged. It will almost certainly meet with a higher-than-necessary degree of failure and make it quite difficult to determine where improvements can be made.

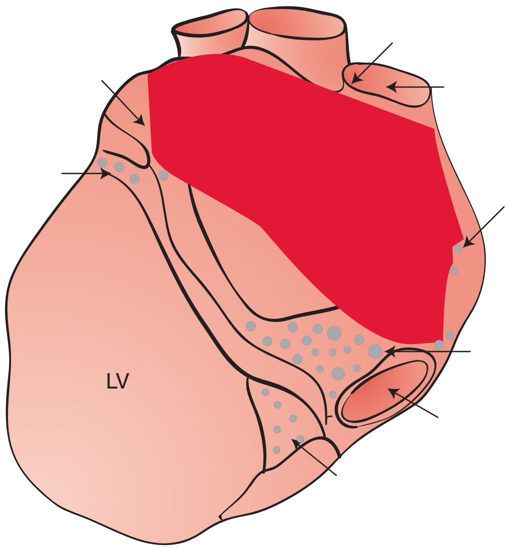

Figure 22–1 Illustration of a "box" lesion placed on the posterior wall of the left atrium (dark red area), completely surrounding the pulmonary veins as a pedicle. The view is posterior, showing the aorta and pulmonary artery superiorly and the left ventricle inferiorly. The superior and inferior vena cavae are to the right and the left atrial appendage is to the left. (LV, left ventricle.)

THE FUTURE OF SURGICAL THERAPY

There has been a marked reduction in the number of cut-and-sew Maze operations, but the number of ablative procedures performed during open heart surgery for the treatment of atrial fibrillation has skyrocketed, entirely because newer technologies have become available (see Fig. 22–2). It is reasonable, therefore, to expect that new ablative devices will become, much more widely used as time goes by and as their safety, effectiveness, and ease of use become widely known. At this point, it is not clear what technology (or technologies) should be used, on which patients, and for what pattern of lesions.

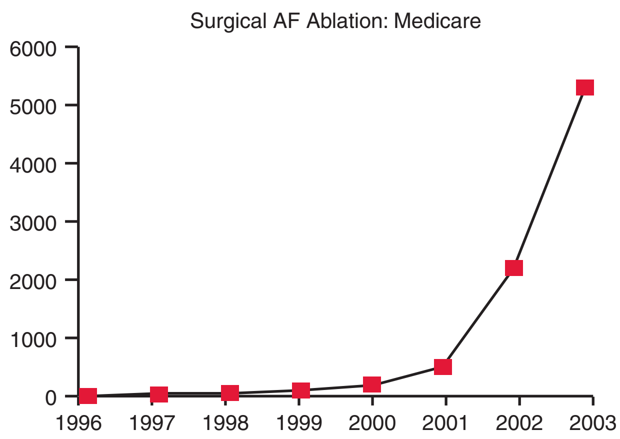

Figure 22–2 Medicare data from 2004 showing the rate of increase of surgical atrial fibrillation cases performed over a 7-year period.

The Case for Concomitant Therapy

The justification for treating AF in patients about to undergo open-heart surgery is an easy one: If an effective and safe procedure can be performed, then it is indicated. As stated earlier, although thousands of ablative procedures have been performed using a number of different technologies to create lesions, there have been no organized, prospective, controlled studies addressing the issues of technology or lesion selection. The literature consists of case reports, small retrospective series, and an occasional prospective registry-type report. Despite this, the results have been generally gratifying and complication rates have been low.[40]

The Data Supporting Treatment

There is an interesting and common misconception in the surgical community that patients with valvular disease and AF will be cured of their AF if the valve issues solely are addressed. This is clearly not the case, and a unique opportunity will have been forfeited if concomitant therapy is withheld. Elahi and coworkers showed in a group of 877 patients undergoing isolated coronary bypass surgery that if they came to the operating room in AF, only 5% regained sinus rhythm at their 1-year anniversary.[41] Raine and colleagues followed 92 patients undergoing isolated mitral valve replacement and found that only 8.5% of those starting in AF returned to SR.[42]

Remaining in AF after cardiac surgery is not benign: The odds for suffering stroke were 3.4 times higher if AF is the predominant rhythm after mitral surgery[43] and 2.2 times higher after aortic surgery.[44] Furthermore, the presence of AF after valve surgery proved to be an independent risk factor for heart failure and death.[45]

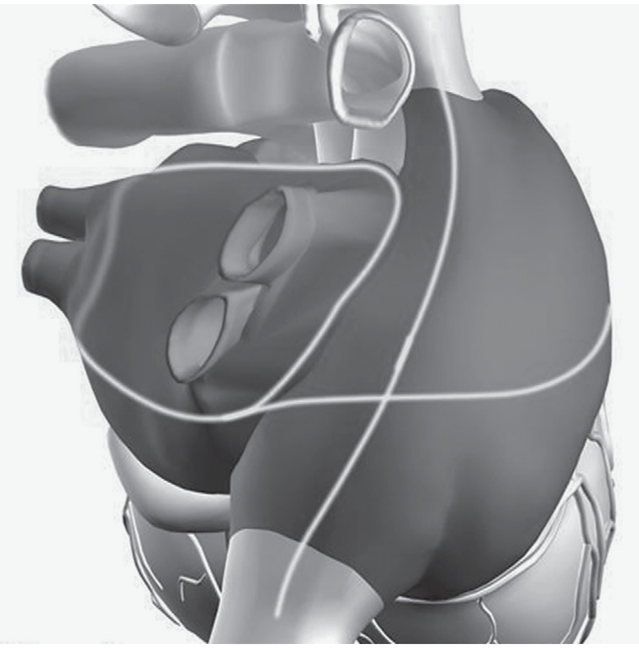

Figure 22–3 Illustration of right atrial lesions placed on the free wall of the right atrium and between the two vena cavae. The box lesion encircling the pulmonary veins can also be seen.

Is return to sinus rhythm beneficial? In Bando's series of 241 patients who underwent either mitral valve or aortic valve surgery with a combined Maze procedure, survival improved over the 5-year follow-up period if sinus rhythm was restored.[46] The incidence of stroke likewise decreased from 19.1% to 6.4% with sinus rhythm. Return to sinus rhythm was also associated with a fall in pulmonary artery pressures[47] and improvements in left atrial size and function.[48] Clearly, because the patients with valvular disease are the most likely to have AF at the time of surgery, they will benefit the most from concomitant treatment and it should be offered to them. Although patients with isolated coronary disease might not benefit as much as those with valvular disease, if they too can undergo ablation with minimal risk it should be offered to them.

A Review of the Available Technologies

The classic lesion creation method is cutting and sewing tissue. This creates a scar composed mostly of collagen and little-to-no cellular material. It is, therefore, not electrically conductive. The goal of "alternative technologies" has been to create a similar scar by thermal injury and coagulation necrosis. To produce such an injury, the tissue must be either heated to 50°C or frozen to –60°C. The quantity of tissue injured is usually directly proportional to the duration of time during which the tissue is held at either temperature. The various energy sources discussed below differ mainly in the method by which they transfer energy to the tissue and how deeply that energy is conducted into the tissue.

A summary review of some characteristics, advantages, and disadvantages of each method is given in Table 22–1. It should be noted that at present (2006) the devices discussed as follows are all FDA-labeled for the ablation of soft tissues (all except the Atricure device are also labeled for cardiac muscle ablation) but *none* is approved for the treatment of AF. Therefore, they are all currently being used "off-label" for the treatment of AF.

Despite clearly different energy forms and application methods, it is interesting to note that when applied with the left atrium open, from the endocardial aspect with full cold cardioplegic arrest, there seems to be very little difference in the safety or efficacy of any one device over the others.[40]

The most extensive experience has been with the dry unipolar RF devices, mainly Boston Scientific's Cobra probe. The probe consists of a malleable 6 cm long × 2 mm diameter active tip that can be shaped as the operator desires. Surveying its reported use in 16 studies including 1187 patients, Khargi and his colleagues found that dry unipolar RF was effective at freeing patients from AF 78% of the time (reported success ranged from 42% to 92%).[40] There have been several complications attributed to the use of the probe; the most worrisome were esophageal injuries, resulting in death 60% of the time.[40a] As more experience has been gained with the device and safer methods of ablation have been developed—such as placing a cold, wet sponge between the posterior wall of the left atrium and the esophagus and/or shielding the probe in nonconducting sheaths—these injuries should become rare.

There are many energy sources available to the surgeon and no overwhelming advantages or disadvantages to any one of them. The choice is mainly up to the person performing the procedure; however, there may be some points to consider in

Table 22–1 Characteristics, Advantages, and Disadvantages of Each Method of Tissue Ablation in Use by Cardiac Surgeons in 2005

Energy Source	Method	Advantages	Disadvantages	Brand name
Dry Unipolar RF	Contact resistive heating	• Well-understood technology • High tissue temperatures achieved • Flexible delivery system	• Poor temperature control • Fat does not heat well or conduct well • No transmurality feedback • Dosimetric energy delivery • Collateral damage from conduction into surrounding structures	Boston Scientific Cobra
Irrigated Unipolar RF	Contact resistive heating	• Higher energy delivery at lower operating temperature • Small tip can make many lesions • Complete operator control over lesion set	• Highly operator-dependent (otherwise same as dry unipolar RF)	Medtronic Cardioblate
Dry Bipolar RF	Contact resistive heating	• Shielded energy source • Very localized lesion • Possible transmurality feedback, used to control energy delivery • Very fast ablation times	• Fixed device shape, limiting lesion types • Large device, making minimal access difficult	Atricure
Irrigated Bipolar RF	Contact resistive heating	• Device more malleable than dry bipolar RF • Irrigation avoids char (otherwise as with dry bipolar RF)	Same as dry bipolar RF (except more flexible delivery system)	Medtronic Cardioblate BP
Microwave	Radiation into tissue	• Shielded energy source • Flexible probe • Penetrates fat well • Does not require direct tissue contact	• Dosimetric energy delivery • No transmurality feedback	Guidant Flex 4 and Flex 10
High-intensity focused ultrasound	Radiation into tissue	Same as microwave	Same as microwave	St. Judes Medical Epicor
Laser	Radiation into tissue	Same as microwave	Same as microwave	Edwards Lifesciences OptiWave
Cryothermy	Direct tissue freezing	• Wide safety margin (otherwise as with microwave)	• Question about energy "sink" problems (otherwise similar to microwave)	Cooper Medical Frigitronics; CryoCath SurgiFrost

RF, radiofrequency.

selection: If the device can only be used from the endocardium, then it likely will not be useful in treating patients with only coronary artery disease or only aortic valve disease in whom the left atrium will not routinely be opened. Conversely, if the device can be used from either the epicardium or endocardium, then more patients could be treated. If the device is rigid, with a fixed shape, then it cannot be used to make lesions of arbitrary shape or size unless access is established to the endocardium and, even then, such lesions may not be possible. A malleable device can be used on any patient and from any approach. If the device emits energy in one direction only ("unipolar"), then there is currently no way to know precisely when an endpoint such as transmurality has been reached. Bipolar clamp devices follow specific algorithms that are designed to stop ablation when transmurality has been achieved.

Ablative Therapy of Lone Atrial Fibrillation

Since its development more than 15 years ago, very few Maze operations have been used for the treatment of lone AF, despite its demonstrated efficacy and safety. This lack of enthusiasm has been largely due to its invasiveness, its risks, and the daunting prospect of a prolonged recovery from open-heart surgery. In an effort to make ablative therapy more palatable to patients and referring physicians, surgeons have been making significant efforts at miniaturizing the Maze procedure, mostly through the use of small access incisions and alternative ablative technologies, such as those discussed earlier. This is a worthwhile goal because it is quite unlikely that the total number of concomitant ablations will ever exceed 40,000 annually (totaling the number of patients with coronary disease and/or valve disease who present in the operating room with AF), whereas there are more than 2 million people suffering with AF in the United States alone.

Currently, fewer than 0.1% of patients with AF receive any form of nonpharmacologic therapy, and it remains unknown exactly how many patients with lone AF might benefit from ablation. However, the case for treating these patients early in their course is easy to defend. Cure rates with pharmacologic therapy have been disappointing and AF is clearly a progressive disease. Between 5.5% and 8.6% of patients who are newly diagnosed with paroxysmal AF progress to more permanent forms over the next 5 years.[48, 49] Because the treatment of AF is much simpler in its paroxysmal stage and because patients are likely to be healthier overall, an ablative treatment offered early would provide them with a safe and lifelong cure.

Less Invasive Procedures

The key to enhancing the adoption of any new procedure is the avoidance of the sternotomy incision. Performing the ablation on the beating heart without the use of cardiopulmonary bypass is desirable although less important. Growing experience and sophistication with minimally invasive surgical techniques have helped with the emergence of two procedures that fit this criterion. One technique uses small thoracotomies and a bipolar RF clamp device, whereas the other employs fully endoscopic methods with a microwave or laser device.

Wolf and associates first described the use of small bilateral thoracotomy incisions and video-assisted methods to electrically isolate the PVs with a bipolar clamp device.[50] Through a 5-cm working incision and two ancillary 10-mm ports, these surgeons were able to surround and electrically isolate the PVs on one side of the heart and then repeat the procedure on the contralateral side for the other PVs. They reported their results in 23 patients followed for more than 3 months with 91% freedom from AF. No complications were reported. The main advantage of this technique is the use of the bipolar clamp device, which has good transmurality feedback guiding lesion creation. It also provides access for managing the left atrial appendage. The main disadvantage is that the procedure can perform only PV isolation. The clamp device cannot connect the PV "loop" lesions to each or perform any other linear lesions without opening the left atrium. The operation also requires repositioning the patient and essentially conducting two separate operations, one on each side of the chest, to obtain full access.

The first procedure employing bilateral simultaneous thoracoscopy was developed and reported by Saltman and colleagues using the Flex 10 microwave device.[51] This completely endoscopic procedure avoids open incisions in the chest, and instead employs port access techniques, varying between 5 mm and 12 mm each. It has been modified by several other surgeons[52] and has now also been used with the OptiWave laser device manufactured by Edwards Lifesciences.

The originally described procedure used six ports, three into the right pleural space and three into the left. The port configuration is shown in Figure 22–4. The most critical part of the procedure is to establish access posterior to the left atrium and to surround the PVs with the ablation device. This is done first through the right pleural space. The right side of the left atrium is accessed through a vertical pericardiotomy, extending from the aorta to the diaphragmatic fat pad, as shown in Figure 22–5. The transverse and oblique sinuses are then entered from the right side using common endoscopic dissecting instruments to remove the fold of pericardium protecting them. Once the sinuses are entered, the Flex 10 ablative element is introduced using guide catheters (Fig. 22–6). The guide catheters are generally not threaded completely around the heart from the right-sided approach because of the possibility of entrapping the left atrial appendage. Rather, they are left in place and retrieved from a left-sided vantage point. If the Flex 10 were to remain medial to the appendage, the proximal circumflex coronary artery would be endangered and the PVs would not be surrounded.

After the guide catheters are positioned, the right lung is inflated and the left lung is deflated. The pleural space is accessed through the ports as indicated in Figure 22–4. The left side of the heart is accessed through a small left pericardiotomy. The guide catheters are retrieved and the final positioning of the device is assured under direct vision by drawing it around the heart under traction. Once the ablation element is in position, it is activated sequentially to create a completely encircling lesion around the PV pedicle and the posterior LA wall. This typically requires 7 to 10 energy applications at 65 W and 90 seconds each. Once the PV pedicle has been isolated, the Flex 10 is withdrawn from the posterior pericardium and placed against the lateral wall of the left atrial appendage such that a lesion is created extending from the transverse sinus out to the tip of the appendage. This requires another 1 or 2 energy applications. The Flex 10 is then either withdrawn from the chest entirely (for treating paroxysmal AF) or access is reestablished from the right side to create right atrial lesions (for treating permanent AF). After the Flex 10 has been withdrawn, the left atrial appendage is removed by stapling with an automatic endoscopic stapler (SurgASSIST, Power Medical Interventions, New Hope, PA). Obliteration of the appendiceal stump is confirmed by transesophageal echocardiography (TEE) guidance. Figure 22–7 shows the intermediate-term success rates for maintaining sinus rhythm.

Ganglionated Plexuses

There has been a great deal of interest in the role of atrial autonomic innervation and its role in the genesis and perpetuation of AF.[53,54] The Oklahoma group has shown that

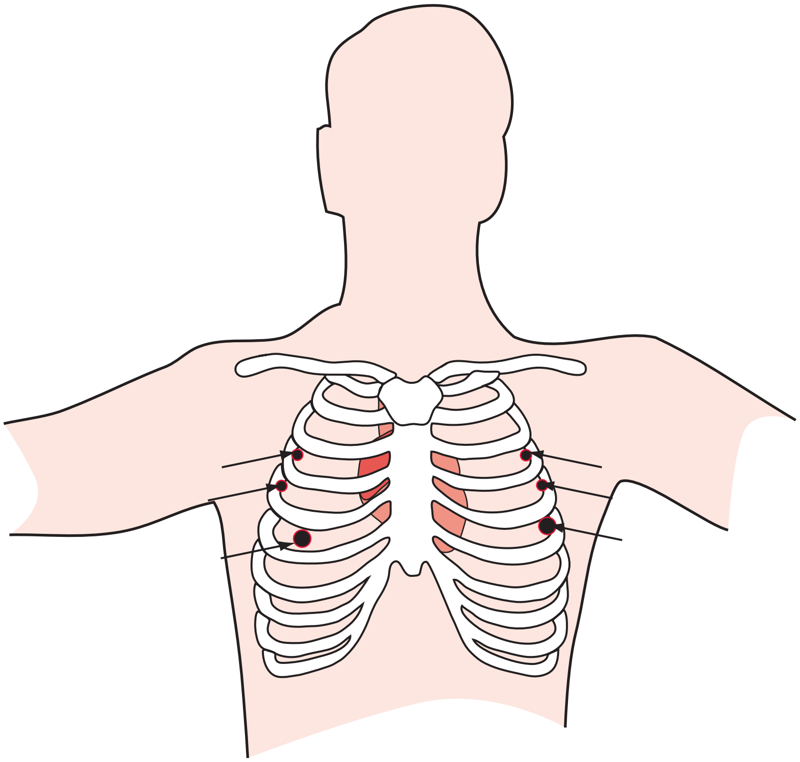

Figure 22–4 Position of thoracoscopic port access points on the chest wall (*arrows*). Typically, six access sites are used: Four 5-mm ports are inserted between the third and fourth intercostal spaces in the anterior axillary line behind the pectoral fold on either side of the chest and two 12-mm ports are inserted between the fifth and sixth intercostal spaces. On the right side of the chest, this lowermost port is located in the anterior axillary line; on the left side it is located in the posterior axillary line to permit optimal positioning of the endoscopic stapler.

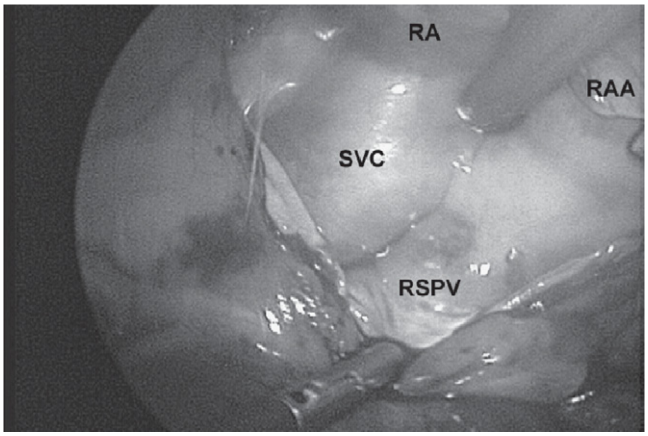

Figure 22–5 Intraoperative photograph taken during thoracoscopic exposure of the right side of the heart. After pericardiotomy, the right-sided structures are exposed, as indicated by labels. For orientation, the patient's head is located to the left of the photograph. (Ao, aorta; RA, right atrial free wall; RSPV, right superior pulmonary vein; SVC, superior vena cava.)

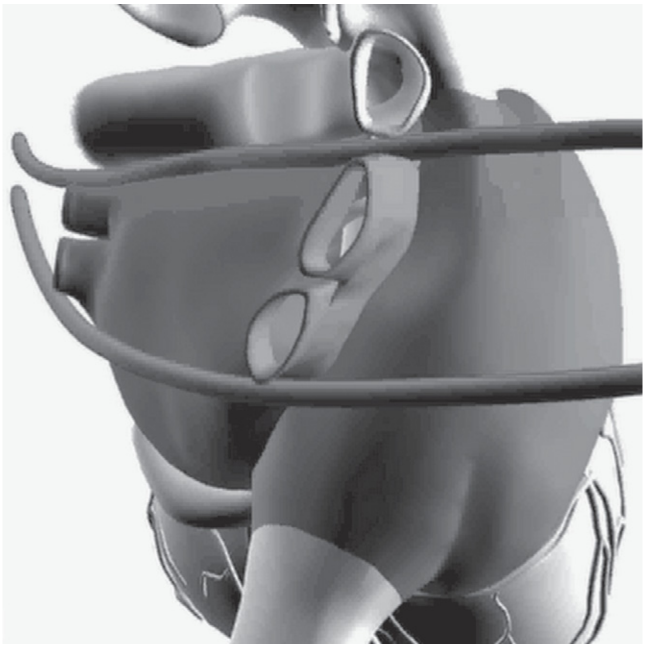

Figure 22–6 Illustration of rubber catheters being placed behind the heart, through the transverse sinus (superiorly) and the oblique sinus (inferiorly) from right to left direction. The catheters are used to guide and position the microwave ablation device completely around the pulmonary vein pedicle.

directed ablation of the ganglionated plexuses located on the epicardial surface of the atrium can increase success at achieving sinus rhythm from 70% to 91%.[55] The exact role of the plexuses, however, is not yet clear and remains the topic of active research; in fact, the concept of controlling AF by ablating them is not new. It is also not yet known how best to ablate them; although it appears that less energy and lower tissue temperatures will be required to destroy the plexuses, thereby being a theoretically safer procedure than full-thickness, transmural muscle ablation.

The ability of minimally invasive epicardial approaches to visualize, test, and ablate the plexuses effectively gives them a significant advantage over endocardial, catheter-based methods. Ablation over the plexuses can be accomplished easily (almost automatically) with a flexible encircling probe;

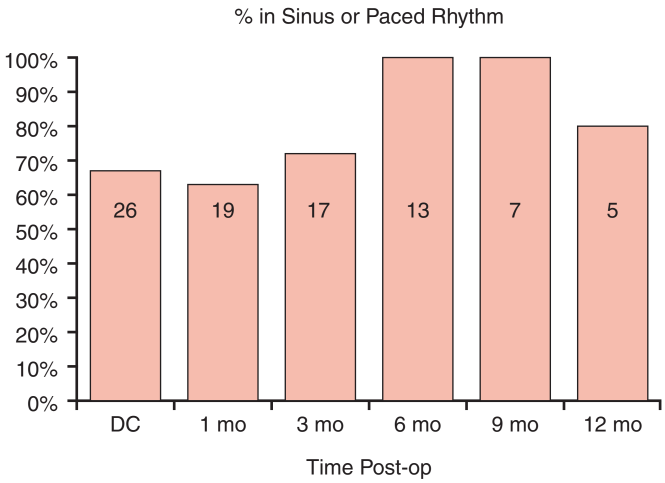

Figure 22–7 Percentage of patients achieving freedom from atrial fibrillation on routine ECG after endoscopic microwave ablation, as measured from time of operation. DC, hospital discharge.

in contrast, plexus destruction with a bipolar clamp is not possible and requires adjunctive measures such as bipolar forceps coagulation.

Hybrid Procedures and the Future

Although the early results of these minimally invasive procedures appear promising, there are clearly some problems that may permanently hinder complete success. Foremost among these is the general inability of any epicardial method to create a lesion from the PVs toward and including the mitral valve annulus. This lesion has long been believed to be critical at preventing atypical left atrial flutter from appearing, but has been shown in a series of concomitant ablation cases to enhance long-term success.[56]

Considering the amount of fatty tissue located epicardially to the mitral annulus, as well as the fact that vascular structures such as the coronary sinus and terminal branches of the left circumflex coronary artery traverse the same region, it is doubtful that ablation from the epicardium will ever be safe or even possible. Ablation from the endocardial surface, however, has been performed often in the electrophysiology laboratory and in the operating room without adverse experiences. Therefore, it is logical to assume that the best approach to the mitral annular lesion would be endocardial, given current technology. Perhaps in the near future the PV isolation and LA appendage management could be carried out from the epicardium and the mitral annular lesion would be created from the endocardium.

Before such a simultaneous, combined approach can be widely adopted, it must balance the risk of failure to prevent AF without the mitral annular lesion against the risk of the left-sided catheter-based approach (transseptal puncture, intracardiac imaging, cardiac chamber perforation, thromboembolism, atrioesophageal fistula, and so on). For example, if 80% to 90% of patients would be cured without the mitral lesion, is it justified to perform many unnecessary catheter ablations? Or should only those patients who show failure after 3 to 6 months of follow-up have a mitral lesion added?

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Chapter 23

Acute and Chronic Pharmacologic Management of Supraventricular Tachycardias

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CHAPTER CONTENTS

Drug therapy remains an important component in both the short- and long-term management of patients with supraventricular tachycardias. The appropriate use of drugs in these patients requires an understanding of the electrophysiologic mechanisms and pathways responsible for each particular arrhythmia, the pharmacology of the tissue or tissues involved, and the properties of the drugs themselves. Drugs may be used both as immediate therapy to terminate episodes of tachycardia or in chronic prophylactic therapy to maintain sinus rhythm long term. The most common supraventricular tachycardias involve reentry over a single circuit, and a very short duration of drug effect may be all that is necessary to break the tachycardia episode. Prophylaxis of recurrent arrhythmias requires a different strategy than that for termination. In reentrant arrhythmias, complete and permanent conduction block in the circuits involved is achievable only rarely, and if the tissue is required during normal conduction, fixed block may not be desirable. Effective strategies may include facilitation of early termination via rate-related block in the atrioventricular (AV) node, drug-induced changes in conduction times, or production of block only in abnormal, nonvital conduction pathways. Long-term suppression of automatic arrhythmias often requires approaches to eliminate or modify precipitating stimuli or to suppress or eliminate selectively the responsible tissues. This chapter deals primarily with therapy for paroxysmal supraventricular tachycardia (PSVT) and atrial flutter.

PHARMACOLOGY OF SUPRAVENTRICULAR TACHYCARDIAS

Drug therapy of supraventricular arrhythmias is typically based on the concept of a "vulnerable parameter" that can be the primary target of drug action.[1] The sinus node and the AV node have calcium-mediated action potentials and are more sensitive to direct effects of calcium channel blockers and adenosine and indirect (autonomically mediated) effects of adenosine, β-adrenergic blockers, or cardiac glycosides. Atrial muscle will have conduction depressed by sodium channel blockers and refractory periods prolonged by potassium channel blockers. Enhanced or abnormal automaticity in atrial muscle may be due to many mechanisms; therefore adenosine, β-adrenergic antagonists, calcium channel blockers, and sodium channel blockers may all be effective in selected cases. Most accessory pathways have electrophysiologic properties similar to those of atrial or ventricular muscle. Conduction and refractory periods of accessory pathways are most susceptible to sodium and potassium channel blockers, but some pathways sensitive to adenosine have been described. Although there are limitations to the Vaughan Williams classification of antiarrhythmic drugs,[2] it may still be useful as a general guide for the selection of drug therapy (Table 23–1 and Appendix 1, Cardiovascular Drugs: Comprehensive Drug Tables).

EVALUATION OF THERAPY

Several types of studies have been used to establish the effectiveness of drug therapy in patients with supraventricular arrhythmias. The most reliable studies are randomized trials comparing the study drug with either a placebo control or a second active agent. The range of doses studied during the course of drug evaluation should include both minimally and maximally effective doses. When two agents are compared, it is important that each drug be tested at doses expected to produce a maximal or near-maximal response.

For acute termination of an episode of tachycardia, the efficacy of a drug is relatively easy to evaluate. Patients presenting with an appropriate arrhythmia are entered into the trial. Both spontaneous and stimulation-induced episodes of arrhythmia may be included. After an observation period to establish stability of the tachycardia, the patient is administered one or more doses of the drug under study or the active or inactive control. Total response is determined by the proportion of episodes converted within a specified period of time. The maintenance of normal rhythm after conversion for some specified period of time can serve as a secondary endpoint.

The prevention of arrhythmia induction in an electrophysiologic study during drug therapy is rarely used as an endpoint in patients with supraventricular arrhythmias for several reasons. First, radiofrequency ablation has become pri-

Table 23–1 Drug Actions in Supraventricular Arrhythmias

	Electrocardiography				Electrophysiology		
Class and Agents	PR	QRS	QT_c	JT_c	AV	AP	AVN
Na^+ channel blockers Ia (quinidine, procainamide, disopyramide)	NC	(↑)	↑	↑	ERP, ↑ COND, ↓	ERP, ↑ COND, ↓	ERP, NC COND, NC
Ic (flecainide, propafenone, moricizine)	↑	↑↑	(↑)	NC	ERP, ↑ COND, ↓↓	ERP, ↑ COND, ↓↓	ERP, ↑ COND, ↓
β-Adrenergic blockers (many preparations)	↑	NC	NC	NC	ERP, NC COND, NC	ERP, NC COND, NC	ERP, ↑ COND, ↓
K^+ channel blockers* (amiodarone, sotalol, dofetilide)	↑	NC	↑↑	↑↑	ERP, (↑) COND, ↑	ERP, ↑ COND, ↑	ERP, ↑ COND, ↓
Ca^{2+} channel blockers (verapamil, diltiazem)	↑	NC	NC	NC	ERP, NC COND, NC	ERP, NC COND, NC	ERP, ↑↑ COND, ↓↓
Adenosine	↑	NC	NC	NC	ERP (A), ↓ ERP (V), NC COND, NC	ERP, ↓ COND, ↑	ERP, ↑↑ COND, ↓↓
Digoxin	↑	NC	NC	NC	ERP (A), ↓ ERP (V), NC COND, NC	ERP, ↓/NC COND, ↑/NC	ERP, ↑ COND, ↑

*Clinically available agents have other actions not related to K^+ channel blockade.
↓, decreased; ↑, increased; ↑↑, marked increase; ↓↓, marked decrease.
A, atrium; AP, accessory pathway; AVN, atrioventricular node; COND, conduction velocity or capability; ERP, effective refractory period; JT_c, corrected JT; NC, no change; QT_c, corrected QT; V, ventricle. Parentheses indicate slight effect.

mary therapy for many supraventricular arrhythmias owing to its high success rate and low complications. The administration of a drug that blocks conduction in the target tissue during the study might interfere with the primary goal of the procedure. Second, the role of autonomic nervous system influences on arrhythmia initiation and maintenance may be profound, and in many cases, changes in autonomic tone can override drug effects.[3] Additionally, protocols for the initiation of supraventricular tachycardias and the correlations between changes in response to stimulation and clinical efficacy are not well established.

Most of the common forms of PSVT are now treated with catheter ablation when that modality is available. Therefore, there are only limited contemporary data about chronic drug therapy for common varieties of PSVT. When placebo-controlled studies have been performed, they usually have used endpoints such as the total number of episodes and the time to first recurrence.[4,5]

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Paroxysmal supraventricular tachycardia (PSVT) is a common arrhythmia with a prevalence of about 2.5 per 1000 adults.[6-8] PSVT in the absence of structural heart disease can manifest at any age but most commonly first occurs between ages 12 and 30 years. In most patients, PSVT due to atrioventricular nodal reentrant tachycardia (AVNRT) or atrioventricular reentrant tachycardia (AVRT) is not causally associated with structural heart disease although exceptions exist (e.g., Ebstein's anomaly, familial preexcitation with cardiomyopathy). Atrial tachycardias may occur either in structurally normal or abnormal hearts. In normal patients, the physical examination during PSVT is significant mainly for the rapid heart rate. Prominent jugular venous pulsations due to atrial contraction against closed AV valves may be a clue that AVNRT is the mechanism. The patient's history, physical examination, and ECG constitute an appropriate initial evaluation. Further diagnostic studies are indicated only if signs or symptoms that suggest structural heart disease are present.

MECHANISMS OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Figure 23–1 schematically illustrates the common forms of PSVT.[7] The AV node sits in the triangle of Koch in the floor of the right atrium. Separate pathways, characterized by their conduction velocities as fast or slow, provide input into the AV node. If these pathways have different refractory periods, reentry using one pathway for anterograde conduction and one for retrograde conduction may occur. The P wave position during AVNRT depends on the types of pathways used. In the most common form, slow pathway—anterograde, fast pathway—retrograde, the P wave is either not seen or is visible

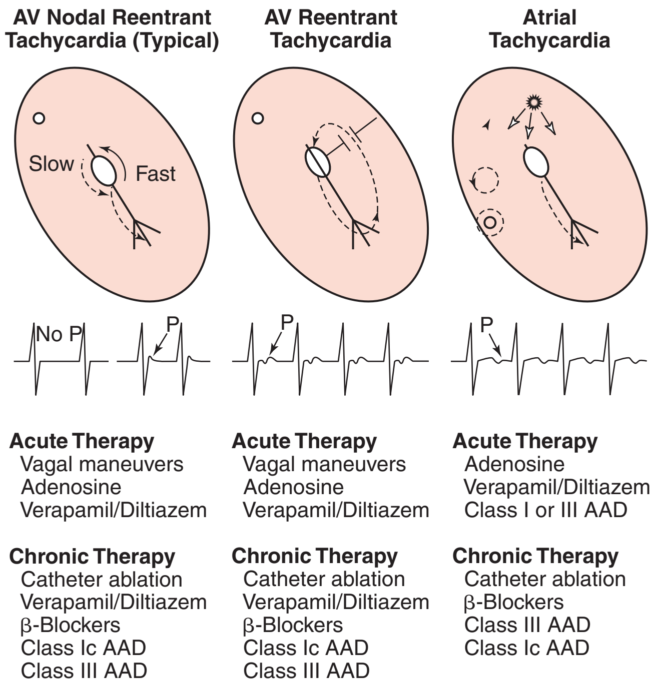

Figure 23–1 Schematic illustration of the common forms of PSVT. AV, atrioventricular, AAD, antiarrhythmic drug. (Adapted from Ferguson JD, DiMarco JP: Contemporary management of supraventricular tachycardia. Circulation 2003;107:1096-9.)

in the terminal portion QRS. If two slow pathways or if a fast anterograde and slow retrograde pathways are used, the RP' interval will either be short or long, respectively. Although uncommon, AV block is possible during tachycardia if the block occurs distal to the turnaround point where the pathways join.

In AVRT, an extranodal accessory pathway connects the atrium and ventricle. Accessory pathways may exhibit both anterograde and retrograde conduction, or either only antegrade (uncommon) or retrograde conduction. In the latter situation, the pathway is called a "concealed" pathway. When the pathway manifests anterograde conduction, a delta wave will be present on the surface ECG, and a diagnosis of Wolff-Parkinson-White syndrome is made if the patient has PSVT. Accessory pathways usually manifest rapid AV conduction with no change in conduction velocity over a range of cycle lengths, but a minority of pathways may manifest slower conduction with a decreased velocity at faster rates. The most common form of AV reentry, orthodromic AVRT, uses the accessory pathway as the retrograde limb and the AV node-His as the anterograde limb, resulting in a narrow QRS. Functional or fixed bundle branch block, a reversal of the circuit (antidromic AVRT), or the presence of two accessory pathways can lead to a wide QRS complex during PSVT owing to AV reentry. Accessory pathways can also conduct as passive bystanders during AVNRT or atrial tachycardias, but these patterns are uncommon. In AVRT the ventricle is an obligate part of the circuit, and thus AV block cannot occur.

Atrial tachycardia is the least common form of PSVT in normal individuals but may predominate in patients who have significant atrial scarring, especially those who have undergone earlier atrial surgery. Atrial tachycardias may be due either to enhanced or triggered automaticity or to reentry. Because the AV node and ventricle are not required participants in the arrhythmia, AV block commonly occurs if there is a short atrial cycle length. The PR or apparent RP' intervals depends on the response of the AV conduction system to the atrial rate. P wave morphology depends on the site of origin in the atrium. If the site of origin is within or involves the sinus node region, the terms sinus node reentrant or inappropriate sinus tachycardia are often applied.

Management of Acute Episodes of Paroxysmal Supraventricular Tachycardia

PSVT rarely is so poorly tolerated that it requires immediate termination with electrical cardioversion. Most episodes can be managed with physiologic maneuvers or drugs. The most common types of PSVT require intact 1:1 AV nodal conduction for continuation and are classified as AV nodal-dependent tachycardias. Because the refractory period of the AV node may be modified by vagal maneuvers and by many pharmacologic agents, and because prolongation of AV nodal refractoriness can lead to transient block, AV nodal conduction is the "weak link" targeted by most acute therapies.

Many patients learn to terminate acute episodes of PSVT by employing vagal maneuvers early during the episode. Valsalva is the most effective technique for adults, but carotid massage may be effective.[6] Facial immersion is the most reliable method for infants. Vagal maneuvers are less effective once a sympathetic response to PSVT has become established; therefore patients should try them soon after onset.

Oral antiarrhythmic drug tablets are not reliably absorbed during rapid PSVT,[9] but some patients may respond to self-administration of crushed medications. In one small study,[10] a combination of diltiazem (120 mg) plus propranolol (80 mg) was shown to be superior to placebo and flecainide (about 3 mg/kg). Hypotension and bradycardia after termination are rare complications of this approach in otherwise healthy individuals, and the need for parenteral therapy may be eliminated.

Adenosine and the non-dihydropyridine calcium antagonists, verapamil and diltiazem, are the intravenous drugs of choice for termination of PSVT.[6,7] Adenosine is an endogenous purine nucleoside that slows AV nodal conduction and results in transient AV nodal block when administered during an episode of PSVT (Fig. 23–2).[11] Conduction in rapidly conducting accessory pathways is not affected by adenosine, but pathways with long refractory periods or slow conduction may exhibit block. Exogenous adenosine is cleared extremely rapidly from the circulation by cellular uptake and metabolism with an estimated half-life of <5 seconds. Adenosine effect is typically seen 15 to 30 seconds after rapid peripheral infusion as a first-pass effect. Administration via a central line requires dose reduction. The effective dose range in adults is 2.5 to 25 mg. If no upper dosage limit is imposed, at least transient termination of AV node-dependent PSVT can be produced in all patients. The recommended adult dosage is 6 mg followed, if needed, by a 12-mg dose. In pediatric patients, the

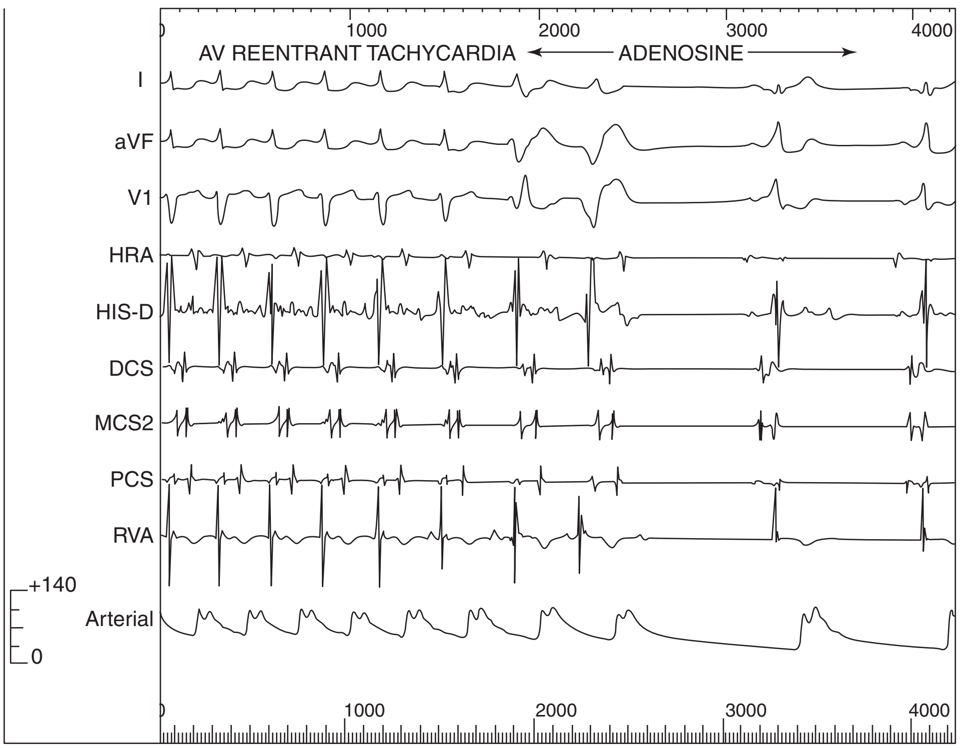

Figure 23–2 Termination of AV reentrant tachycardia with adenosine. The tracings (*from top to bottom*) represent ECG leads 1, aVF and V_1, intracardiac recordings from the high right atrium (HRA), the distal bundle of His (HIS-D), the distal, mid, and proximal coronary sinus (DCS, MCS2, and PCS) and the right ventricular apex (RVA), a femoral arterial pressure and time lines. Adenosine, 6 mg, was infused several seconds before this recording. Note that the tachycardia breaks as AV conduction blocks without a decrease in blood pressure. The first beats after termination show preexcitation over a left-sided accessory pathway.

dose range is 50 to 250 mcg/kg using an upward dose titration. Because of the ultrashort duration of action, cumulative effects of sequential doses are not seen.

Minor side effects that include transient dyspnea or chest pain are common with adenosine. Sinus arrest or bradycardia may occur but resolves quickly if appropriate upward dose titration is used. Atrial and ventricular premature beats are frequently seen with PSVT termination. A few patients with adenosine-induced polymorphic ventricular tachycardia and ventricular fibrillation have been reported.[11,12] The majority of these patients had long baseline QT intervals during tachycardia and had long pauses during adenosine-induced AV block that led to bradycardia-dependent polymorphic VT. Adenosine shortens the atrial refractory period, and atrial ectopy may induce atrial fibrillation. (Fig. 23–3) This may be a dangerous situation if the patient has an accessory pathway capable of rapid anterograde conduction. Because adenosine is cleared so rapidly, re-initiation of PSVT after initial termination may occur. Repeat administration of the same dose of adenosine or substitution of a calcium channel blocker (see later) is likely to be effective.

Adenosine mediates its effects via a specific receptor cell surface receptor, the A_1 receptor. Theophylline and other methylxanthines block the A_1 receptor. Caffeine levels seen after beverage ingestion do not usually interfere with the effect of adenosine. Dipyridamole blocks adenosine elimination, thereby potentiating and prolonging its effects. Cardiac transplant recipients are also unusually sensitive to adenosine. If adenosine is chosen in the latter situations, much lower starting doses (i.e., 1 mg) should be selected.

The AV-node action potential is calcium channel-dependent, and the non-dihydropyridine calcium channel blockers, verapamil and diltiazem, are very effective for terminating AV node-dependent PSVT.[7,11,12] The recommended initial dosage of verapamil is 5 mg intravenously over 2 minutes, followed in 5 to 10 minutes by a second 5 to 7.5 mg dose. The recommended initial dosage of diltiazem is 20 mg followed, if necessary, by a second dose of 25 to 35 mg. PSVT termination should occur within 5 minutes of the end of the infusion, and more than 90% of patients with AV node-dependent PSVT respond to the dosages just listed.

As with adenosine, transient arrhythmias that include atrial and ventricular ectopy, atrial fibrillation and bradycardia may be seen after PSVT termination with calcium channel blockers. Persistent hypotension may occur with calcium channel blockers, particularly if the PSVT does not terminate. Calcium channel blockers are not recommended in infants and neonates with PSVT owing to reports of cardiovascular collapse.[13] Extreme bradycardia after PSVT termination can be seen if calcium channel blockers are given to a patient who has just been loaded with an intravenous β-adrenergic blocker. Adenosine and verapamil have been shown to have equivalent efficacy in several randomized clinical trials.[14-16] Most PSVT patients can be acutely managed with either agent (Table 23–2). To minimize the potential for adverse effects, adenosine should be selected for patients with severe hypotension or heart failure, for infants and neonates, and for those at risk for severe bradycardia. Verapamil and diltiazem should be chosen for patients with poor venous access, for patients with bronchospasm, and for those on agents that interfere with adenosine action or metabolism. Patients with more than a single recurrent episode may do better on a calcium channel blocker compared with multiple bolus injections of adenosine.

AV node-dependent PSVT can manifest with a wide QRS complex in patients with fixed or functional aberration or when an accessory pathway is used for antegrade conduction. However, most wide complex tachycardias are due to mechanisms that may worsen after IV administration of adenosine and calcium channel blockers. Unless there is strong evidence

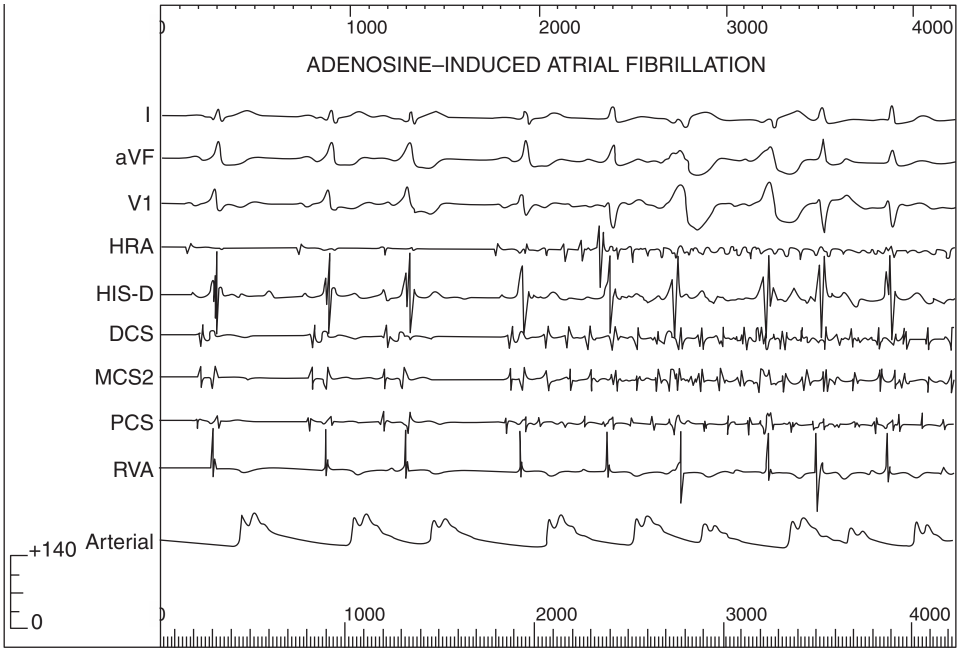

Figure 23–3 Adenosine-induced atrial fibrillation. The tracings are also from the patient shown in Figure 23–2 and were recorded about 15 seconds later. Atrial fibrillation occurs and conduction over both the accessory pathway and the normal conduction system during atrial fibrillation is seen.

Table 23–2 Acute Therapy for PSVT

Adenosine Preferred	Neutral	Calcium Blocker Preferred
Neonates	Routine PSVT	Poor IV access
Hypotension	Central line*	Dipyridamole*
Uncertain diagnosis		Transplant*
Prior IV β-blocker		Theophylline

*Dose reduction for adenosine required.
IV, intravenous; PSVT, paroxysmal supraventricular tachycardia.

that a wide QRS tachycardia is AV node-dependent, test doses of adenosine, verapamil, or diltiazem should not be used.

There are only limited data on the acute pharmacologic therapy of atrial tachycardias.[17] Automatic or triggered atrial tachycardias and those due to sinus node reentry are likely to terminate with adenosine, verapamil, diltiazem, or β-adrenergic blockers. Tachycardias caused by scar-related atrial reentry are more likely to manifest AV block with an unchanged atrial cycle length after administration of these agents.

A selective adenosine A_1 receptor agonist, tecadenoson (CVT-510), is currently undergoing clinical studies.[18,19] This agent can terminate acute episodes of AV nodal-dependent PSVT and may be associated with fewer side effects because it avoids the vasodilatation and bronchoconstriction that can be seen with adenosine itself.

Chronic Therapy of PSVT

Patients with well-tolerated episodes of PSVT, that always either terminate spontaneously or can be broken quickly and reliably by the patient, do not require chronic prophylactic therapy. Selected patients may be treated only for acute episodes as mentioned earlier. For other PSVT patients, either catheter ablation or chronic drug therapy may be appropriate. Current guidelines consider catheter ablation to be the treatment of choice for patients with more than minimal symptoms.[6] Previously asymptomatic patients with preexcitation may also benefit from ablation if they have inducible PSVT at electrophysiologic study.[20] A treatment algorithm we follow is shown in Figure 23–4.

Pharmacologic Therapy

For AV node-dependent PSVT, calcium channel blockers and β-adrenergic blockers will improve, but rarely totally eliminate, symptoms in 60% to 80% of patients.[8,9] Flecainide (50 to 100 mg twice daily) and propafenone (150 to 300 mg twice daily) have effects on both the AV node and the accessory pathways and will also reduce episode frequency.[21,22] These agents can be used safely if patients with ischemic heart disease and/or congestive heart failure are excluded from therapy.[23] Sotalol (80 to 320 mg daily in divided doses), dofetilide (125 to 500 mcg twice daily), and amiodarone (100 to 200 mg daily) should be considered second-line agents.[6] Because sympathetic stimulation can antagonize the effects of many antiarrhythmic agents, concomitant therapy with a β-adrenergic blocker may improve clinical efficacy.

Pharmacologic treatment strategies for atrial tachycardias have not been well evaluated in controlled clinical trials. Depending on the mechanism responsible for the arrhythmia, β-adrenergic blockers, calcium channel blockers, and class I or class III antiarrhythmic drugs may reduce or eliminate symptoms. Scar-related atrial tachycardias, particularly those associated with earlier surgery for congenital heart disease, may be particularly difficult to control. In selected patients, it may be necessary to use AV nodal blocking agents to control ventricular rates during ongoing tachycardia.

Atrial Flutter

Clinical investigations during the last 15 years in patients with atrial flutter have greatly expanded our understanding of this relatively common arrhythmia.[6] In atrial flutter, the ECG will

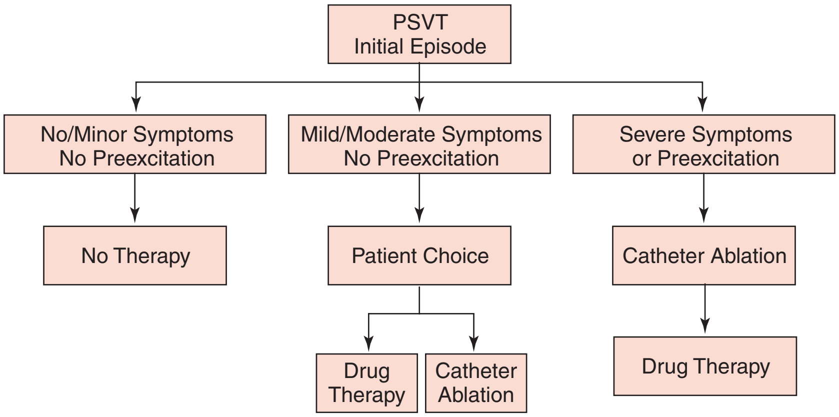

Figure 23–4 Algorithm for the management of paroxysmal supraventricular tachycardia (PSVT).

show an organized atrial rhythm at a rate of 300±50 beats per minute. Patients with atrial flutter share many characteristics with patients with atrial fibrillation, and many patients will manifest both arrhythmias. In most cases, atrial flutter is due to reentry over a large, well-defined circuit within the atria. In classic atrial flutter, a counterclockwise circuit is present in the right atrium, of which the cavotricuspid isthmus forms a crucial portion. In classic or typical atrial flutter, this circuit produces an ECG pattern with negative flutter waves in the inferior leads and a positive atrial deflection in lead V_1. The same isthmus-dependent circuit can also be used in a clockwise fashion with reversal of these ECG findings. Because the atrial cycle length in atrial flutter is less than the refractory period of the AV node, 2:1 or greater block is most commonly seen but 1:1 conduction may be seen if adrenergic tone is high or if the flutter cycle length is relatively slow. Other ECG patterns in atrial flutter may also be observed. Some atrial flutters, although still isthmus dependent, will involve circulation around the inferior vena cava owing to conduction across the *crista terminalis*, a pattern described as "lower-loop reentry."[6,24,25] If the reentry circuit does not involve the cavotricuspid isthmus, the patient is said to have atypical flutter, and a variety of ECG patterns may occur, some of which can mimic the patterns seen in typical atrial flutter.

Atrial flutter can manifest with a wide range of symptoms that are largely dependent on ventricular rate. Some patients may be asymptomatic, despite a ventricular rate of 150 beats per minute and 2:1 AV block. Patients with advanced forms of heart disease may not tolerate atrial flutter even when ventricular rates can be controlled.

Acute Management of Atrial Flutter

Management of the patient who presents with atrial flutter may involve termination of the arrhythmia, ventricular rate control, and steps taken for prevention of thromboembolism. Although data specifically relating to patients with atrial flutter are limited, guidelines for the prevention of embolic events in patients with atrial flutter are the same as those for patients with atrial fibrillation.

As with other arrhythmias, the immediate management strategy for patients with atrial flutter will depend on the clinical situation, the patient's symptoms, and the patient's hemodynamic status. Cardioversion with a direct current shock is highly effective in atrial flutter but is rarely required as an urgent intervention and does not protect against recurrence. Rapid atrial pacing is also quite effective. Stable rate control in atrial flutter is often difficult to achieve because concealed conduction in the AV node is not prominent at the cycle lengths seen in atrial flutter. Intravenous diltiazem and verapamil may slow the ventricular rate, but their effects may be transient and hypotension may complicate therapy.[26-28] Intravenous β-adrenergic blockers and amiodarone may also be used for rate control in critically ill patients. Selected patients with conduction system disease may achieve stable ventricular rates during drug therapy for atrial flutter, but most patients will require termination of the arrhythmia.

Although several antiarrhythmic drugs have been reported to be effective for terminating atrial flutter, the response rates in clinical practice are often disappointing. Class III drugs have been the most successful, presumably because they slow conduction velocity and prevent wavelength shortening.[29] Intravenous ibutilide (1 to 2 mg) is the agent that has been studied most thoroughly. In placebo-controlled trials, ibutilide has shown efficacy rates of 38% to 76%.[30,31] Ibutilide has been shown to be superior to both procainamide and sotalol.[6,30,31] The major problem with ibutilide is a risk of proarrhythmia. About 1% to 2% of patients in clinical trials of ibutilide developed QT prolongation and sustained polymorphic ventricular tachycardia. Nonsustained ventricular tachycardia episodes after ibutilide occur with an incidence of 1.8% to 6.7%. Assessment of serum potassium levels and the QT interval are important steps to take before ibutilide administration. Pretreatment with intravenous magnesium before ibutilide infusion would be a reasonable precaution but has not been systematically studied. Intravenous dofetilide is also quite effective for conversion of atrial flutter but is available now only in an oral formulation.[32] The class Ic agents, propafenone and flecainide, have limited efficacy in atrial flutter,[29] and, should they slow the atrial cycle length, may allow 1:1 AV conduction with a paradoxical increase in ventricular rate.

Long-Term Management of Atrial Flutter

Atrial flutter is less commonly recurrent or persistent than atrial fibrillation. Few data are available that specifically focus on the long-term efficacy of drug therapy for atrial flutter. Long-term rate control may be an option in selected patients who have intrinsic conduction system disease. In most others, concealed conduction in the AV node is not prominent owing to the regularity of the atrial cycle length and, as a result, effec-

tive long-term rate control is usually difficult to maintain.[6] The approach to prophylactic drug therapy in atrial flutter is similar to that used in patients with atrial fibrillation (see Chapter 21). If class Ia, class Ic, or class III drugs are used, AV nodal-blocking agents are usually also prescribed to protect against 1:1 conduction, should atrial flutter recur with a cycle length prolonged by the drug. Dofetilide has been shown to be somewhat more effective in patients with atrial flutter as compared with patients with atrial fibrillation.[32]

As discussed in Chapter 20, catheter ablation of isthmus-dependent atrial flutter is often the therapy of choice for many patients. This procedure, in which a linear ablation line is drawn from the tricuspid valve isthmus to the inferior vena cava and/or eustachian valve, is highly (more than 90%) successful in the short term. Although early recurrence rates were found to be high when this technique was first employed, this was probably due to incomplete lesions that failed to produce complete bidirectional isthmus block. Current techniques have reduced the incidence of recurrence of typical atrial flutter after the initial ablation procedure. However, many patients, particularly those who have associated structural heart disease, will remain at risk for developing atrial fibrillation despite a previously successful ablation for atrial flutter.[33,34]

Multifocal Atrial Tachycardia

Multifocal atrial tachycardia is characterized by three or more distinct P wave morphologies at an irregular rate that ranges from 110 to 180 beats per minute. It is usually associated with a severe underlying illness—often respiratory insufficiency or methylxanthine toxicity. Rate control is difficult because there is little concealed conduction in the AV node, and the patient's background sympathetic tone is often high. β-Adrenergic blockers may slow the rate but are often contraindicated by bronchospasm. Intravenous calcium channel blockers often produce hypotension. High-dose intravenous magnesium has been reported to facilitate conversion, but hypotension and nausea may complicate the effect.[35] Therapy is, therefore, best directed at the underlying disease process. AV junctional ablation and pacemaker insertion may be required for selected patients.

Inappropriate Sinus Tachycardia

Inappropriate sinus tachycardia may be diagnosed when a persistent, nonparoxysmal tachycardia with a P wave morphology identical to that seen in sinus rhythm is present during the waking hours.[36] Secondary systemic causes should be excluded. Typical symptoms include palpitations, dizziness, fatigue, dyspnea, and chest pain. β-Blockers are the usual agents selected initially for therapy, but some patients will respond to verapamil or diltiazem. Total relief of symptoms with drug therapy alone is unusual.

JUNCTIONAL ECTOPIC TACHYCARDIA

This rhythm occurs primarily in infants and children. A congenital form and the more common postoperative form have been described.[37,38] The congenital form usually manifests with congestive heart failure in infancy. The postoperative form is seen after surgery to repair tetralogy of Fallot, transposition of the great vessels, and other forms of complex congenital heart disease. The mechanism for both arrhythmias is believed to be enhanced automaticity in the AV junction proximal to the region that gives rise to the His potential. Because of the incessant nature of the tachycardia and its resistance to cardioversion and most forms of drug therapy, mortality rates are high when the arrhythmia is seen in critically ill postoperative patients. Limited experience with sotalol, propafenone, flecainide, and amiodarone suggests that trials with these drugs are warranted. In addition, total body cooling may be helpful in postoperative patients. However, catheter ablation with permanent pacing, if needed, may be required for patients who fail to respond to drugs.

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Chapter 24

Atrial Fibrillation

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CHAPTER CONTENTS

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and, in many ways, the most complex to manage. Our understanding of this disorder has increased immensely in the last decade, and new therapeutic options are developing at a rapid pace. AF is increasingly recognized to be a heterogeneous disease that cannot be managed with a "one-size-fits-all" solution. Instead, the approach to the optimal treatment of a patient with AF requires the clinician to address the underlying heart disease and its interactions with potential therapies, the individual's estimated risk of thromboembolism associated with the arrhythmia, and the presence and severity of arrhythmia-related symptoms. The general physician and the cardiologist treating AF should know when to refer the patient for an electrophysiologic intervention, and the cardiac electrophysiologist should know when to offer one of several invasive approaches.

CLASSIFICATION

AF may be classified by the underlying disease,[1] by the frequency and duration of its occurrence,[2] or by a combination of both. *Paroxysmal* AF is defined as a self-terminating arrhythmia, usually lasting less than 48 hours and rarely more than 7 days. *Persistent* AF is an arrhythmia that fails to convert spontaneously but will do so with intervention (usually cardioversion or drug therapy), and *permanent* AF is an arrhythmia that is resistant to conversion to sinus rhythm. "Permanent AF" is the loosest term of the trio because its definition is, in many cases, dependent on the vigor with which the physician pursues sinus rhythm restoration. To these three terms is added the term "*new-onset* AF" that represents the initial documented event, because the outcome of a first episode of arrhythmia is not known. The "three Ps" are not static categories and may merge with one another over time such as when new-onset and paroxysmal AF become sustained in a significant percentage of patients. The presence or absence of symptoms, their severity, and an assessment of whether they are related to inadequate ventricular rate control or to loss of normal AV synchrony are helpful adjuncts to the classification of AF, but it should be recognized that thromboembolic risk is unrelated to the presence or absence of arrhythmia-related symptoms.

The Decision for Rhythm or Rate Control

A series of randomized controlled trials of rhythm control compared with rate control as treatment strategies have been published.[3-6] These studies were generally conducted in older patients with AF and clinical risk factors for thromboembolism but who were minimally symptomatic. The methods varied and, in most instances, anticoagulation in the rhythm control group was not mandated (although it was commonly used). In the largest of these trials, the AFFIRM study,[6] the primary endpoint was mortality, and the uniform finding of all these studies was that neither strategy was superior to the other in terms of any of the primary endpoints. When a post-hoc analysis was done as to outcomes *by rhythm* (regardless of assigned strategy), the presence of sinus rhythm in the AFFIRM trial favored survival, whereas the presence of coronary disease, diabetes, and/or smoking were adverse factors in terms of mortality rate.[7] To maintain sinus rhythm, however, antiarrhythmic agents generally had to be used, and these were associated with a decreased likelihood of survival, which offset any potential benefit of sinus rhythm. Although this observation might be used to argue that an optimal strategy is sinus rhythm maintenance by nonpharmacologic means, the complexity of this retrospective analysis is such that it should be thought of only as an hypothesis-generating observation and not as a well-supported conclusion. Indeed, a subsequent analysis of the RACE trial data failed to demonstrate any benefit of sinus rhythm over AF.[8] Functional status was slightly better in the AFFIRM trial among patients in sinus rhythm, regardless of assigned group.[9]

The trials of rate versus rhythm control treatment strategy are not the last word in this controversy because large groups of patients including the young and very old, those with congestive heart failure, and those with highly symptomatic AF were underrepresented. As a consequence, there is ongoing debate regarding the relative merits of these two approaches.[10,11]

Regardless of the questions left unanswered by these trials, an important and consistent finding was that stroke risk was not reduced by the strategy of rhythm control when compared with the strategy of rate control and anticoagulation. Although most of the patients in both groups received warfarin, it was stopped more often in the group in which sinus

rhythm had apparently been restored; recurrent sustained or paroxysmal AF in this group was most likely responsible for thromboembolic events. Thus, decisions regarding rhythm versus rate control must not be based on the desire to withdraw or withhold warfarin, because recurrence is common and may be both asymptomatic and paroxysmal, rendering its detection on routine examination difficult. Although the decision to attempt to maintain sinus rhythm or to choose rate control should be an individualized decision based on a careful assessment of clinical and echocardiographic features in each patient, patients with severe symptoms and young age are generally preferred candidates for attempted rhythm control, whereas older patients with minimal symptoms may be equally, if not better, served by a rate control strategy.

Rate Control

In patients with new-onset AF, the average ventricular response is 100 to 150 beats per minute.[12] The irregular R-R intervals are associated with a marked variation in stroke volume,[13,14] and this possibly contributes to the uncomfortable sensation of AF with a poorly controlled heart rate. With stimuli that result either in vagal tone withdrawal or an increase in sympathetic tone such as exertion, fever, hyperthyroidism, or blood loss, the ventricular rate in AF may increase markedly. Thus, a good rule of thumb for the clinician is to ask "If this patient were in sinus rhythm, would he or she have sinus tachycardia?" If the answer is "yes," then the rapid ventricular response may reflect the presence of a condition that will need to be corrected before rate control can be achieved.

For some patients, particularly those with paroxysmal AF, a rapid ventricular response is associated with uncomfortable symptoms, most commonly palpitations or dyspnea.[15] In persistent AF, a disproportionate rise in heart rate with exertion may lead to dyspnea or fatigue.

Pharmacologic Rate Control in Atrial Fibrillation—What Is the Optimal Ventricular Rate?

Control of the ventricular rate in AF has a twofold aim: elimination of symptoms and improvement of cardiac efficiency. As heart rate increases in AF, stroke volume tends to decrease, but cardiac output is generally maintained over a relatively wide range, probably decreasing when mean heart rate exceeds 110 to 120 beats per minute.[16] However, a higher resting heart rate probably is inefficient because it is associated with a higher myocardial oxygen demand. Thus, it is appropriate to attempt to reduce heart rate during AF.

The AFFIRM investigators defined adequate rate control as an average heart rate < 80 beats per minute at rest and either a maximum heart rate <110 beats per minute during a 6-minute walk ***or*** an average heart rate during 24 hours of ambulatory monitoring <100 beats per minute, with no heart rate greater than 110% maximum predicted age-adjusted exercise heart rate.[17] Using this definition, β-blocking agents were the most effective initial drug for rate control, with a 70% success rate if used either alone or with digoxin compared with 54% for calcium channel antagonists and 54% with digoxin alone.[17] These results document in an older population with cardiac disease the apparent superiority of β-blockers. They also show that digoxin alone, although not effective in everyone, still has a role to play in heart rate control in patients with AF. Furthermore, digoxin is synergistic with both calcium channel blockers and β-blockers and may decrease the required dosages of these agents and decrease their associated side effects.[18]

It is also important to recognize that tighter heart rate control based on the number of beats per minute does not necessarily translate into improved symptoms. Although calcium channel antagonists are less effective than β-blockade for heart rate control, trials of β-blockers in patients with sustained AF have failed to show an improved exercise tolerance. Moreover, if peak heart rate is excessively blunted, exercise tolerance may decrease.[19]

Traditionally, when considering agents for ventricular rate control in AF, the discussion is usually separated into β-blocking agents, calcium channel antagonists, and digoxin, as if each of these classes of agents were mutually exclusive (Table 24–1). Although monotherapy may be effective in a significant number of patients, the addition of digoxin and an intermediate dose of a β-blocker or a calcium channel blocker may produce excellent heart rate control, even though a high-dose single agent has failed. Evaluation of information from the AFFIRM trial shows that physicians frequently use a combination of agents for heart rate control and that combination therapy seems to have a greater likelihood of tight rate control compared with monotherapy with any agent.[17] In a small but well-designed crossover trial, it was shown that the addition of digoxin to either diltiazem or to a β-blocker resulted in superior rate control than when any of these agents was used as monotherapy.[18] Caution should, however, be exercised in using such combinations because the negative chronotropic effects of the combination may produce significant sinus bradycardia should sinus rhythm return. If verapamil is chosen, the verapamil-digoxin interaction is likely to necessitate a lower dose of digoxin than would be required if used alone or with diltiazem.[20]

Nonpharmacologic Approach to Rate Control

Interruption of AV nodal function with catheter ablation and concomitant pacemaker implantation is a highly effective strategy for rate control. It is a relatively simple procedure that is associated with a significant and sustained improvement in quality of life.[21] Data suggest, however, that, at least in the setting of impaired ventricular function, right ventricular pacing may be harmful.[22,23] Such a realization has tempered enthusiasm for this procedure except in cases where pharmacologic management proves impossible.

Rhythm Control

The strategy of rhythm control involves the restoration and maintenance of sinus rhythm. AF may spontaneously revert to sinus rhythm or may persist indefinitely unless cardioversion is performed. Spontaneous cardioversion occurs most often within 48 hours of arrhythmia onset.[24] If spontaneous cardioversion does not occur, sinus rhythm can be restored through the use of antiarrhythmic drugs or DC electrical cardioversion. Before cardioversion, appropriate precautions need to be taken to prevent thromboembolic events.

Table 24–1 Pharmacologic Heart Rate Control in Atrial Fibrillation

Drug	Control of Acute Episode	Control of Sustained AF	Comments
Calcium Channel Blockers			
Diltiazem	20 mg bolus followed, if necessary, by 25 mg given 15 min later. Maintenance infusion of 5-15mg/hr	Oral controlled-release diltiazem 180-360 mg daily	Long-term rate control may be better with the addition of digoxin.
Verapamil	5-10 mg IV over 2-3 min repeated once, 30 min later. Maintenance infusion rate is not reliably documented	Slow release verapamil 120-240 mg release once or twice daily	Causes elevation in digoxin level. May have more negative inotropic effect than diltiazem.
β-Blockers*			
Esmolol	0.5 mg/kg IV, repeated if necessary. Follow with infusion at 0.05 mg/kg/min, increasing as needed to 0.2 mg/kg/min	*Not available in oral form*	Hypotension may be troublesome, but responds to drug discontinuation.
Metoprolol	5 mg IV bolus repeated twice every 2 minutes. No data on maintenance infusion	50-400 mg daily in divided doses	Useful if concomitant coronary disease present.
Propranolol	1-5 mg IV (given over 10 minutes)	30-360 mg in divided doses or as long-acting form once daily	Noncardioselective: caution with history of bronchospasm
Digoxin	1.0-1.5 mg IV or PO over 24 hours in increments of 0.25 to 0.5 mg	0.125-0.25 mg daily	Renally excreted. Slow onset of action intravenously, with less effective control than other agents, although may be synergistic with them. Least effective agent, but may be acceptable monotherapy in sedentary patients.

*Several other oral β-blockers have similar efficacy for rate control.
AF, atrial fibrillation; IV, intravenous/intravenously.

Pharmacologic Cardioversion

Intravenous and oral drugs are available for pharmacologic cardioversion (Table 24–2). Pharmacologic cardioversion is most successful when used within 24 to 48 hours of onset of AF.[25] The use of pharmacologic agents for conversion should be followed by electrical therapy if this approach fails. The currently available intravenous agents in the United States are procainamide and ibutilide. The success rate of these agents for the conversion of AF is poorer with procainamide than with ibutilide, and ibutilide is superior for the conversion of atrial flutter than for AF.[26]

Caution must be used when administering these drugs owing to the risk of torsades de pointes (TDP) with either agent (as high as 3% to 5% with ibutilide),[27] and hypotension with procainamide.[26] Patients must be monitored for proarrhythmia for at least 2 hours following the termination of the infusion.

An alternative approach to intravenous therapy is the use of high-dose oral antiarrhythmic drugs for the conversion of AF to sinus rhythm. Quinidine, in an initial dose of 200 mg, repeated in a dose of 200 mg every 2 hours for 3 separate doses, has a high success rate for conversion,[28] but it has fallen into disfavor because of a high incidence of side effects, including TDP.[29] High-dose oral therapy has been widely studied, using high doses of type IC medications (450 to 600 mg of propafenone[30] or 300 to 400 mg of flecainide).[31,32] These drugs should be avoided in patients with bundle branch block, structural heart disease, or ventricular preexcitation. There is a risk of proarrhythmia including atrial flutter with 1:1 AV nodal conduction and hemodynamic collapse, as well as ventricular tachycardia.

The initial administration of these drugs should be in a monitored setting with the capability for defibrillation. If found to be successful without adverse effects, oral therapy can subsequently be used as a self-administered approach by selected patients with a structurally normal heart (the so-called "pill-in-the-pocket" approach).[33] Oral amiodarone has been extensively studied for the conversion of AF. It has been shown to be safe to load during AF in the outpatient setting and is associated with a rate of successful cardioversion of up to 80% after 24 hours in AF of 48 hours duration or less[34] (although the success rate is much lower for arrhythmia of longer duration).[35]

Electrical Cardioversion

Electrical cardioversion for AF can restore sinus rhythm in >90% of instances.[36] Successful cardioversion is defined as the restoration of sinus rhythm if even for only one beat, and it is inversely related to the duration of AF and the size of the left atrium. Biphasic defibrillator waveforms are more successful than monophasic waveforms,[37] and anteroposterior electrode

Table 24–2 Recommended Doses of Drugs Proven Effective for Pharmacologic Cardioversion of Atrial Fibrillation

Drug*	Route of Administration	Dosage†	Potential Adverse Effects
Amiodarone	Oral Intravenous/oral	Inpatient: 1.2 to 1.8 g per day in divided dose until 10 g total, then 200 to 400 mg per day maintenance or 30 mg/kg as single dose Outpatient: 600 to 800 mg per day divided dose until 10 g total, then 200 to 400 mg per day maintenance 5 to 7 mg/kg over 30 to 60 min, then 1.2 to 1.8 g per day continuous IV or in divided oral doses until 10 g total, then 200 to 400 mg per day maintenance	Hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)
Dofetilide	Oral	Creatinine Clearance (mL/min) — Dose (mcg BID) More than 60 — 500 40 to 60 — 250 20 to 40 — 125 Less than 20 — Contraindicated	QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age
Flecainide	Oral Intravenous	200 to 300 mg‡ 1.5 to 3.0 mg/kg over 10 to 20 min‡	Hypotension, atrial flutter with high ventricular rate
Ibutilide	Intravenous	1 mg over 10 min; repeat 1 mg when necessary	QT prolongation, torsades de pointes
Propafenone	Oral Intravenous	600 mg 1.5 to 2.0 mg/kg over 10 to 20 min‡	Hypotension, atrial flutter with high ventricular rate
Quinidine§	Oral	0.75 to 1.5 g in divided doses over 6 to 12 h, usually with a rate-slowing drug	QT prolongation, torsades de pointes, GI upset, hypotension

*Drugs are listed alphabetically.
†Dosages given in the table may differ from those recommended by the manufacturers.
‡Insufficient data are available on which to base specific recommendations for the use of one loading regimen over another for patients with ischemic heart disease or impaired left ventricular function, and these drugs should be used cautiously or not all in such patients.
§The use of quinidine loading to achieve pharmacologic conversion of atrial fibrillation is controversial, and safer methods are available with the alternative agents listed in the table.
AF indicates atrial fibrillation; BID, twice a day; GI, gastrointestinal; and IV, intravenous.
Adapted from ACC/AHA/ESC: Guidelines for the management of patients with atrial fibrillation. Circulation 2006;114:e257-e354.

positioning is somewhat more successful than anterolateral placement, although this is not a consistent finding.[38,39] The immediate reversion to AF after either a single beat of sinus rhythm or seconds to minutes of sinus rhythm occurs in about 12% of patients[40] and is termed the early recurrence of AF (ERAF[41]). It may be prevented by antiarrhythmic drugs such as ibutilide.[42,43]

If cardioversion fails at the maximum energy output of the device, a second shock at the same energy level a minute or so later may succeed because the level of transthoracic impedance falls with each shock. Alternatively, a change to another orientation will occasionally be successful. Application of pressure to the anterior electrode will also diminish the transthoracic impedance and improve success rates.[44] Finally, pretreatment with an intravenous or oral antiarrhythmic drug can facilitate cardioversion by lowering defibrillation thresholds and reducing early recurrence of AF.[42,43]

MAINTENANCE OF SINUS RHYTHM

Pharmacologic Approaches

Antiarrhythmic drugs are widely prescribed for the maintenance of sinus rhythm. In general, these agents have a similar efficacy, with about a 50% rate of recurrence of symptomatic AF at 1 year compared with about 20% to 25% maintenance of sinus rhythm in the absence of antiarrhythmic drugs. Amiodarone has consistently been shown to be more efficacious than other available antiarrhythmic drugs with a 75% rate of AF suppression at 1 year.[45] If one agent fails to maintain sinus rhythm, a second agent may be successful, particularly one from another group of drugs.[46] It is unrealistic to expect complete suppression of AF with any of these agents. Instead, the goal should be a significant reduction in the frequency of AF compared with pretreatment patterns.

Table 24–3 Antiarrhythmic Drugs, Dosages, and Toxicities

Drug	Dose (24hr)	Cardiac Toxicity	Noncardiac Toxicity	Recommended Monitoring and Drug Interactions
Amiodarone	200-400 mg (initial load 600-1200 mg for 1-2 weeks). Choose lower dosing for smaller and older patients	Bradycardia, TDP (rare)	Pulmonary toxicity,* photosensitivity, hepatic toxicity,* GI upset and neurologic toxicity (dose related), thyroid dysfunction,* Rise in INR with warfarin	LFTs q 6 months PFTs at baseline and only with symptoms of potential toxicity CXR yearly TFTs: baseline, 3 mos, then q 6 mos. Potentiates warfarin, digoxin, dilantin, tricyclics
Dofetilide	500-1000 mcg	TDP	NS	In-hospital initiation for 72 hrs, creatinine clearance q 3 months QT interval. Levels increased by multiple drugs (e.g., verapamil)
Sotalol	160-320 mg	TDP, CHF, sinus bradycardia	Bronchospasm	QT interval
Flecainide	200-300 mg	Ventricular tachycardia, atrial flutter with 1:1 conduction	Dizziness	NS
Propafenone	450-900 mg	Ventricular tachycardia, atrial flutter with 1:1 conduction	Metallic taste	NS
Quinidine	600-1500 mg	TDP, enhanced AV nodal conduction	Thrombocytopenia, fever, nausea, diarrhea	QT interval Platelet count Will increase digoxin levels Can potentiate warfarin
Procainamide	1-4 g	TDP	Agranulocytosis, lupus-like syndrome	QT interval NAPA increased by ethanol
Disopyramide	400-750 mg	TDP, CHF	Urinary retention, dry mouth, contraindicated if existing glaucoma	QT interval

AV, atrioventricular; CHF, congestive heart failure; CXR, chest x-ray; GI, gastrointestinal; INR, International Normalized Ratio; LFTs, liver function tests; NAPA, *N*-acetyl procainamide; NS, not significant/not stated; PFTs, pulmonary function tests; TDP, torsades de pointes; TFT, thyroid function tests.

The major toxicities of antiarrhythmic drugs include both proarrhythmia and noncardiovascular adverse effects. The noncardiovascular toxicities differ by drug and range from benign changes in taste to life-threatening pulmonary or liver toxicity (Table 24–3). Antiarrhythmic drugs alter cardiac sodium and/or potassium channel function either to slow conduction (sodium channel blockers) or to prolong the refractory period (potassium channel blockers).[47] Prolongation of the refractory period (prolongation of repolarization) results in QT prolongation, which may be excessive if dosing is too high; if excretion is reduced, if there is a genetic predisposition to a prolonged QT or if the patient has genetically prolonged drug metabolism.[48] Prolongation in conduction such as that produced by the IC agents causes QRS prolongation, which is more marked at faster heart rates.[49] QT prolongation may result in TDP,[49,50] and antiarrhythmic drugs that block the delayed rectifier potassium channel (IK_r and/or IK_s) may cause TDP in up to 5% of patients.[49] Drug-related TDP is more likely to occur in association with slow heart rates, electrolyte abnormalities (hypokalemia or hypomagnesemia), female gender, unrecognized congenital long QT syndrome, and pauses associated with the conversion of AF to sinus rhythm.[51] The concomitant use of drugs that interfere with the hepatic metabolism of antiarrhythmic drugs may also result in QT prolongation.[52] Reduced urinary clearance of renally excreted medications may also result in toxicity.[53] In some instances, such as with sotalol or dofetilide, the risk of TDP is proportional to blood levels and related to renal excretion;[54] with quinidine, it is idiosyncratic and not dose related. A metabolite of procainamide, *N*-acetyl procainamide, prolongs the QT interval,

	Lone AF	Depressed LV function/ Congestive heart failure	Coronary artery disease, Normal LV function	Hypertrophic cardiomyopathy
First Line	Flecainide Propafenone	Amiodarone Dofetilide	Sotalol Amiodarone	Amiodarone Sotalol
Second Line	Sotalol Amiodarone Dofetilide Type 1A		Dofetilide Type 1A	Dofetilide
Avoid		Flecainide Propafenone	Flecainide Propafenone	

Figure 24–1 Algorithm for the choice of antiarrhythmic drug based on the patient's clinical characteristics.

whereas the parent compound has little effect on repolarization. Slow acetylators produce less *N*-acetyl procainamide and have a lower risk of TDP. Rapid acetylators develop more *N*-acetyl procainamide and are more prone to TDP.[55]

Ventricular tachycardia may occur in patients taking antiarrhythmic drugs. This complication is well described in patients who take type IC medications (flecainide and propafenone) and who have had a prior myocardial infarction and impaired ventricular function.[56] Atrial flutter with a slow atrial rate and 1:1 AV nodal conduction that produce a widened QRS duration with hemodynamic collapse may also occur, particularly with class IC drugs.[57] This latter complication can generally be avoided with the addition of atrioventricular nodal blocking medications.

Bradyarrhythmias develop most often as a result of sinus node suppression or slowing of conduction through the atrioventricular node. Both of these complications are more frequently seen in elderly patients with underlying sick sinus syndrome.[58] Ambulatory monitoring (see later) and appropriate dose reduction or drug discontinuation can prevent serious consequences.[59]

Choice of Drug

The toxicity of antiarrhythmic drugs can be reduced by the careful selection of agent with regard to the patient's clinical history. Briefly, the risk factors for adverse effects include left ventricular hypertrophy, myocardial scarring (most commonly due to earlier myocardial infarction), and left ventricular systolic dysfunction. The presence of any of these clinical features should be evaluated before choosing an antiarrhythmic drug (Fig. 24–1). For patients without structural heart disease, the choice of drugs is wider, but it is still important to evaluate noncardiac comorbidity.

Initiation and Monitoring of Antiarrhythmic Drugs

The toxicity of antiarrhythmic drugs can be reduced with the appropriate choice of dose and method of monitoring during the loading phase. For example, unexpected bradycardia can often be avoided by reducing the usual loading dose of amiodarone or starting with a low dose of sotalol and increasing to therapeutic dose as tolerated. This strategy is particularly important in patients with suspected sinus node dysfunction.

Some controversy exists regarding the need for in-hospital initiation of antiarrhythmic drugs for the treatment of AF. The major concern is the precipitation of TDP. This proarrhythmic effect occurs in drugs that prolong repolarization and is almost never seen with flecainide and propafenone. In-hospital monitoring for 72 hours is incorporated into the drug labeling of dofetilide and is, therefore, mandatory for this drug, regardless of the presence or absence of structural heart disease.[60] Quinidine is rarely used owing to its significant and idiosyncratic propensity for provoking TDP,[61] but it is an effective atrial antiarrhythmic agent. Experimental data suggest that the risk of TDP can be reduced by the concomitant use of verapamil. Two large trials of quinidine for either paroxysmal AF or the maintenance of sinus rhythm after an episode of persistent AF demonstrated that, when it was combined with verapamil, it was as effective as sotalol with less risk for TDP.[62,63] As noted earlier, a pause associated with the conversion of AF to sinus rhythm may promote the development of TDP. Consequently, in patients with paroxysmal AF, it is advisable to initiate antiarrhythmic drugs with the potential for TDP while the patient is in sinus rhythm.

In contrast to QT-prolonging agents, in-hospital initiation of type IC agents (which should only be used in patients with a structurally normal heart) and amiodarone (which may be used in any form of heart disease) is generally not required. There is considerable experience with the initiation of amiodarone in the outpatient setting during AF, without significant toxicity.[35,59,64] QT prolongation is common with amiodarone, but it is not generally associated with a large risk of TDP (<1%) unless the corrected QT interval is significantly prolonged (>500 milliseconds).[65]

The concern with type IC agents is the conversion of AF to atrial flutter with 1:1 conduction to the ventricles and hemodynamic instability. It is, therefore, strongly recommended that atrioventricular nodal blocking agents be used in conjunction with a type IC agent.[66] Particular caution should be exercised for patients who are athletic because the development of atrial flutter during exercise may be associated with 1:1 conduction even in the presence of digoxin or calcium channel blockers. Theoretically, the antisympathetic aspects of β-blockade should be more effective in such patients.

Amiodarone may be initiated in the outpatient setting during AF, given the widespread safety data with this practice. If there is no congestive heart failure and if the patient is

in sinus rhythm, it may be possible to initiate other antiarrhythmic drugs, with the exception of dofetilide, in the ambulatory setting. To increase the safety of this approach, patients can be monitored with a continuous event recorder. The transmission of a single 30-second tracing daily permits monitoring for bradycardia, QT prolongation, and tachyarrhythmias. This protocol is continued for 10 days and has been shown to be quite effective.[59]

Despite safe initiation of an antiarrhythmic drug, the long-term possibility of proarrhythmic effects still exists. It is, therefore, important that physicians and patients are aware of circumstances that may render previously tolerated medications to be dangerous. Examples of these situations include the initiation of diuretics or certain antibiotics in patients taking QT-prolonging drugs, and the development of renal dysfunction in patients receiving renally excreted antiarrhythmic drugs such as sotalol or dofetilide.

Adjunctive Therapy for the Maintenance of Sinus Rhythm

Advances in the understanding of the electrical and mechanical remodeling of the atrium that occurs during AF have led to the evaluation of drugs that are not primarily antiarrhythmic in nature as an adjunct to maintaining sinus rhythm. The calcium channel blocking agents may blunt electrical remodeling of the atrium, and several trials have evaluated the efficacy in the pericardioversion state. As single agents, diltiazem and verapamil do not appear to prevent recurrence of AF in humans.[67] However, when given for a few weeks before cardioversion and continued for a few weeks after cardioversion of AF in the setting of an antiarrhythmic agent, there appears to be a modest, synergistic benefit.[68] In large clinical trials of losartan versus atenolol for hypertension, AF was reduced in the group treated with these drugs.[69] Several small trials seem to demonstrate a benefit of pericardioversion use of these agents,[70] although the results are more consistent with angiotensin receptor blockers than with calcium channel antagonists.[71] Currently, no specific recommendations regarding the use of calcium channel antagonists, ACE inhibitors, or angiotensin blockers as an adjunctive therapy can be made. However, if a patient with AF for whom cardioversion is considered needs antihypertensive therapy, the use of either an ACE inhibitor or angiotensin receptor blocker seems prudent.

Nonpharmacologic Approaches for the Maintenance of Sinus Rhythm

The invasive approach to the management of AF is rapidly evolving. As noted previously, certain antiarrhythmic agents may transform AF into atrial flutter. Advantage has been taken of this transformation because atrial flutter may be cured by the application of a line of ablation from the tricuspid valve to the inferior vena cava. This so-called "hybrid therapy," defined as the conversion of AF to atrial flutter by an antiarrhythmic drug (most commonly flecainide or propafenone) with subsequent ablation of atrial flutter,[72] is most commonly unplanned and is suitable for only a small number of patients with AF in whom flutter fortuitously occurs.

Percutaneous left atrial ablation is now widely employed for the attempted prevention of AF recurrence. There are multiple permutations of this procedure, but all involve the electrical isolation of the pulmonary veins to prevent atrial premature beats from entering the left atrium and triggering the onset of AF.[73-75] Some clinicians choose to create additional linear lesions in the left atrium to impair the perpetuation of AF, should it become triggered by a nonpulmonary vein source or by an incomplete pulmonary vein isolation (PVI). The optimal ablation procedure and the best choice of patient population for this procedure continue to evolve. Although relatively uncommon, the risks include pulmonary vein stenosis, pericardial tamponade, stroke, and atrial-esophageal fistula formation.[76] This procedure is associated with a 60% to 70% rate of suppression of AF during a 12- to 24-month follow-up period.[77-80] Recurrent AF, which may be reduced in frequency and/or symptoms, is seen in the majority of the remaining patients. Left atrial tachycardia has been noted in 5% to 30% of patients and appears more frequently when additional linear lesions are created.

Studies of arrhythmia surveillance post-PVI have demonstrated significant rates of asymptomatic AF.[81] It is, therefore, necessary to continue anticoagulation in patients with clinical risk factors for stroke, irrespective of the perceived success of the PVI procedure.

The surgical correlate of the percutaneous PVI procedure is the maze procedure. The modern maze procedure is a series of ablations performed on the endocardial surface, most often in conjunction with a coronary artery bypass or valve operation.[82] The left atrial appendage is generally oversewn as part of this procedure. Data on patients with preoperative AF undergoing the maze procedure along with mitral valve surgery showed a 78% to 81% actuarial rate of sinus rhythm at 5 years compared with <10% in a group with mitral surgery but no maze procedure.[83] The efficacy of this procedure has been reported to be substantially higher in patients with paroxysmal AF, and the overall efficacy will vary from center to center depending on the experience of the surgeon and the selection of patients. The obliteration of the left atrial appendage as part of the maze procedure carries the potential additional advantage of reducing stroke risk. Nevertheless, caution must be taken in discontinuing warfarin after this procedure because no data confirm that the combined maze and left atrial ablation obliteration completely abolish thromboembolic risk.

A minimally invasive variant of the maze procedure involves the creation of lesions around the pulmonary veins via a thoracoscopic or mini-thoracotomy approach. The left atrial appendage can be obliterated from the epicardial surface as well. This procedure is under investigation and the long-term efficacy is awaited.

The early recurrence of AF after the surgical maze procedure approaches 30%. These early recurrences do not necessarily predict long-term failure of the primary procedure. To reduce short-term postoperative AF after the maze procedure, amiodarone is often prescribed for 1 to 3 months postsurgery. If AF redevelops after discontinuation of the amiodarone, the procedure is recognized as unsuccessful.

Pacing for the Maintenance of Sinus Rhythm

Current guidelines favor the use of dual- compared with single-chamber pacing to reduce the frequency of AF in

Table 24–4 The $CHADS_2$ Scoring System for Assessing Annualized Stroke Risk

$CHADS_2$ Score	No Aspirin-Adjusted Risk (CI)*	On Aspirin†
0	1.9 (1.2-3.0)	0.8 (0.4-1.7)
1	2.8 (2.0-3.0)	2.2 (1.6-3.1)
2	4.0 (3.1-5.1)	4.5 (3.5-5.9)
3	5.9 (4.6-7.3)	8.6 (6.8-11.0)
4	8.5 (6.3-11.1)	10.9 (7.8-15.2)
5	12.5 (8.2-17.5)	12.3 (6.6-22.9)
6	18.2 (10.5-27.4)	13.7 (2-97)

Risk of stroke per 100 patient-years among patients not receiving warfarin. The score is calculated by assigning 1 point each for **C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes, and 2 points for prior **S**troke or transient ischemic attack. The two columns of data are derived from different cohorts, and the wide confidence intervals with 6 points represent a relatively small number of patients with this score in this cohort. A simplified scheme classifies patients into low stroke risk (score 0), moderate risk (score 1-2) and high risk (score 3-6).
*Data from Gage BF, Waterman AD, Shannon W et al: Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.
†Data from Gage BF, van Walraven C, Pearce L, et al: Selecting patients with atrial fibrillation for anticoagulation: Stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287-92.

Table 24–5 Warfarin Interactions

Potentiate Warfarin	Inhibit Warfarin
Acetaminophen	Azathioprine
Amiodarone	Carbamazepine
Aspirin	Haloperidol
Antibiotics (particularly)	Oral contraceptives
Cephalosporins, ciprofloxacin,	Phenobarbital
erythromycin metronidazole,	Rifampin
trimethoprim-sulfamethoxazole,	Vitamin K-containing
macrolides	foods (green leafy
Cimetidine	vegetables):
Excessive ETOH	spinach, broccoli,
Fluconazole	avocado
NSAIDs	Coenzyme Q
Sulfonamides	St. John's wort
Gingko biloba, ginseng	Hypothyroidism
Congestive heart failure	Nephrotic syndrome
	Edema
	Hereditary coumadin
	resistance

ETOH, ethanol; NSAIDs, nonsteroidal anti-inflammatory drugs.

patients with a history of AF.[84] Efforts to reduce the frequency of AF through alternative site pacing techniques have demonstrated marginal to no benefit. The one exception may be the use of postoperative pacing to prevent cardiac surgery-associated AF.[85,86]

THROMBOEMBOLIC PROPHYLAXIS

Stroke represents the most devastating complication of AF, and the percentage of strokes attributable to this arrhythmia increases with the increasing age of the population.[87] Thus, it is estimated that >35% of strokes in patients >80 years of age are directly attributable to AF.[87] Strokes in patients with AF tend to be more severe than those that result from other causes, such as carotid artery stenosis, and they carry a higher mortality rate.[88,89] Several large trials performed in the late 1980s and early 1990s clearly demonstrated a very significant benefit of warfarin therapy for the prevention of stroke among patients with nonrheumatic AF.[90-97] Paroxysmal AF was shown to have the same annual stroke incidence as persistent AF, and the development of stroke was shown to be an ongoing risk. These trials also defined several subsets of patients with AF who were at a greater risk of stroke than patients in whom the arrhythmia existed in isolation (lone AF). The risk of stroke is greatest in patients with prior stroke or TIA (11% per year), and other risk factors include congestive heart failure, systolic ventricular dysfunction, hypertension (whether current or treated), older age, and diabetes.[98-101] The finding on a transesophageal echocardiogram of dense left atrial spontaneous contrast, diminished left atrial appendage velocities, or complex aortic plaque was associated with a risk of stroke in excess of 13% per year[101-103]; many of these features were associated with the clinical findings noted earlier and transesophageal imaging is not mandatory for risk stratification. Using a simple point system referred to by an acronym such as the $CHADS_2$, an annual stroke estimate can be assessed[100,104] (Table 24–4). For patients deemed to be at moderate-to-high risk of stroke, warfarin is indicated, prescribed to maintain an INR of 2.0 to 3.0. The role of aspirin therapy in AF is less clear. Low-dose aspirin (81 mg) is not effective, and the efficacy of higher dose aspirin (325 mg daily) is controversial.[105,106]

The risk of major bleeding in association with warfarin is low, even in the elderly, if the INR is maintained below 3.0.[107-109] Tight control of the INR can be facilitated by attention to medications and foods that interact with warfarin (Table 24–5). Unfortunately, despite overwhelmingly convincing evidence of the efficacy of warfarin for preventing stroke in AF, a significant number of patients, particularly the elderly, are not prescribed appropriate thromboembolic prophylaxis with warfarin.[110-112] This is due more to a misconception of the risk-benefit ratio of anticoagulation in the elderly, in whom thromboembolic strokes are frequent, often devastating, and sometimes fatal.

Pericardioversion Anticoagulation

The pericardioversion period represents a special situation in terms of thromboembolic risk. After restoration of sinus rhythm, atrial mechanical function may be diminished, and left atrial appendage-emptying velocities may be even lower than they were during AF.[113,114] This occurs more frequently if the duration of AF is long. The return of atrial function generally occurs in 7 to 14 days after restoration of sinus rhythm, and this is a period of high thromboembolic risk. Thus, anticoagulation is mandated during this time, even if a transesophageal echocardiogram showed no thrombus imme-

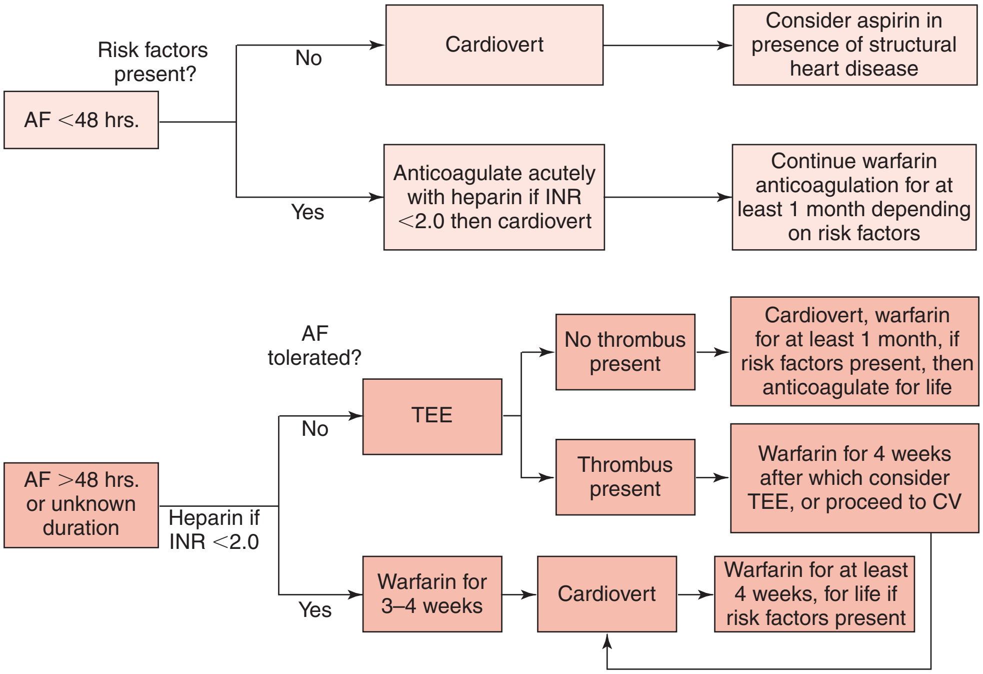

Figure 24–2 Algorithm for anticoagulation pericardioversion.

diately before cardioversion, and even in patients who are deemed not to need long-term warfarin while in AF (i.e., those with lone AF) (Fig. 24–2).[115,116] Current data suggest no clinical benefit to early, transesophageal-guided cardioversion followed by warfarin over a strategy of 3 to 4 weeks of warfarin before cardioversion and continued after cardioversion, although there may be some modest cost savings.[117-119]

ATRIAL FIBRILLATION POSTCARDIAC SURGERY

AF in the postcardiac surgery setting represents a unique situation. AF develops in 30% to 60% of cases and is more likely to occur with valvular surgery than isolated bypass surgery. As with other types of AF, older age is a major risk factor. It most often develops within the first 72 hours after surgery and may be asymptomatic or associated with rapid rates and significant symptoms. Unlike most other types of AF, postoperative AF tends to be self-limited and rarely recurs more than 4 weeks after surgery.

There is a fourfold approach to postoperative AF: (1) perioperative pharmacologic prophylaxis; (2) anticoagulation, if perioperative pharmacologic prophylaxis fails; (3) electrical or pharmacologic termination; (4) ventricular rate control. In addition, several intraoperative measures have been investigated for their effect on prophylaxis of postoperative arrhythmia.

Prevention of postoperative AF, if possible, is the preferred approach . β-Blocking agents have consistently been shown to reduce postoperative AF and should be started preoperatively and continued postoperatively.[120] Amiodarone, ideally in conjunction with β-blockers, seems to be superior to β-blockers alone, but the long half-life of the drug is such that it is best started several days before cardiac surgery.[121,122] As many patients go to cardiac surgery urgently, the optimal use of prophylactic amiodarone is limited to elective patients, and the drug also has significant side effects including postoperative bradycardia and, occasionally, postoperative pulmonary damage. Neither digoxin nor calcium channel antagonists have been shown to prevent postoperative AF, and they should not be used for this indication.[120]

Should a patient develop postoperative AF, the risks of anticoagulation with recent surgery need to be carefully weighed against potential benefits of thromboembolism prophylaxis. No prospective trials have evaluated postoperative anticoagulation as part of the treatment of postoperative AF. Consensus guidelines suggest that heparin should be limited to those patients with postoperative AF who are deemed to be at higher risk of thromboembolism, particularly those who have had a prior stroke or transient ischemic attack. For patients with arrhythmia that has persisted for at least 48 hours, warfarin anticoagulation is recommended (without heparin overlap) with an aim of continuing the drug for approximately 4 weeks after restoration of sinus rhythm.[123] Naturally, extreme care needs to be taken in adjusting anticoagulation in this patient population, and there may be a significant proportion of patients who are deemed to be at a higher-than-average risk of bleeding and for whom anticoagulation is considered inadvisable.

The postcardiac surgery patient may be hemodynamically unstable and, consequently, ventricular rate control in AF is important. On the other hand, many patients already have a relatively well-controlled ventricular response because they are on β-blocking agents, and the concern for ischemia is relatively low, as those with coronary artery disease will have had coronary revascularization.

Intravenous β-blockers and calcium channel blockers (diltiazem and verapamil) have been shown to be effective in controlling ventricular rate in postoperative patients.[124] Digoxin is generally not so effective as the calcium channel blockers or β-blockers as it performs poorly in the setting of high sympathetic tone. However, it may be a useful adjunctive drug for rate control and should certainly be considered in a patient with AF and impaired systolic ventricular function.

There are no trials that compare a strategy of restoration of sinus rhythm in patients with postoperative arrhythmia with that of anticoagulation and rate control to allow for spontaneous resolution of the AF. Should a patient deteriorate with the onset of AF and fail to improve with rate control, electrical cardioversion should be attempted. However, the short-term recurrent nature of postoperative AF often requires an antiarrhythmic agent to maintain sinus rhythm and prevent recurrence. Special considerations about antiarrhythmic agents in the postoperative patient include rapid shifts in electrolytes that might potentially pose an increased risk of TDP, and depressed ventricular function that may increase other proarrhythmic effects. If left ventricular dysfunction is present, amiodarone is considered the drug of choice should conversion to, and maintenance of, sinus rhythm be needed. In patients with normal ventricular function, ibutilide may be used to restore sinus rhythm, but it cannot be used for sinus rhythm maintenance. Sotalol may be a reasonable choice given its β-blocking properties, although excessive bradycardia may occur with sotalol in the postoperative patient.

CONCLUSIONS

The management of AF has undergone considerable change in the last decade and will doubtless continue to evolve. Advances are being made in the field of anticoagulation with the development of direct thrombin inhibitors that do not need constant monitoring[125]; constant refinements are being made in ablation procedures; and new antiarrhythmic drugs are under development. It is likely that the adjunctive therapy of AF will be applied as prophylaxis in high-risk populations and, with all these measures, the goal should be to reverse the increasing incidence and prevalence of this common arrhythmia and to make it easier to treat effectively those patients in whom it still occurs.[126]

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Genetics of Inherited Arrhythmias

Silvia G. Priori and Carlo Napolitano

CHAPTER CONTENTS

Inherited arrhythmogenic disorders are genetically transmitted diseases associated with increased susceptibility to cardiac arrhythmias in patients with structurally intact hearts. They typically manifest with peculiar electrocardiographic patterns, syncope, and sudden death in young, otherwise healthy, individuals. In these conditions, there is a common denominator represented by a genetic abnormality in one of the several proteins that control the excitability of myocardial cells (Fig. 25–1).

In this chapter, we will review the current understanding of molecular pathways and the genetic determinants that predispose to cardiac arrhythmias. We will also summarize the main clinical features of inherited arrhythmogenic diseases and the role of genetic testing in management and risk stratification.

FUNCTIONAL PATHWAYS INVOLVED IN INHERITED ARRHYTHMIAS

Potassium Currents

Potassium currents participate in the control of repolarization of the human heart and determine the resting membrane potential. Over the past 10 years, genes encoding a wide range of pore-forming K^+-channel α-subunits and accessory β-subunits have been cloned, and their electrophysiologic properties have been characterized by in vitro expression in heterologous systems.[1] Subsequently, mutations in some of them have been linked to the pathogenesis of inherited cardiac arrhythmias (see Fig. 25–1). Interestingly, each disease is caused by mutations in different genes, and different mutations within the same gene have been associated with distinct phenotypes, as in the case of "long QT" and "short QT" syndromes. This complex scenario is reviewed in the following sections in which each current implicated in the repolarization of the heart will be discussed, together with the diseases caused in the presence of genetic defects that alter its physiologicl behavior.

Slow Delayed Rectifier (IK_s) Current and Associated Phenotypes

KCNQ1 and *KCNE1* genes encode the α(KvLQT1) and the β(MinK) subunit of the potassium channel that conducts the IK_s current, the slow component of the delayed rectifier current (IK). KvLQT1 is a protein formed by six transmembrane segments that tetramerizes in the membrane to constitute a functional pore-forming unit called the α-subunit of the IK_s channel This α-subunit coassembles with two or more minK subunits, also called β-subunits,[2] to recapitulate the functional channel that conducts the IKs current.[3]

Mutations in the *KCNQ1* and *KCNE1* genes have been identified in patients who are affected by the long QT syndrome (LQTS) (Table 25–1) (http://www.fsm.it/cardmoc). In vitro expression of mutant proteins suggested that they share a common functional result[4] represented by a loss of function. This reduced activity of the channel is either a consequence of haplo-insufficiency or of a dominant negative effect. In genetic diseases that are transmitted as dominant conditions, a "dominant negative effect" is present whenever a mutant protein inhibits the function of the wild-type protein encoded by the wild-type allele.[5] The functional abnormalities observed in patients with mutations in the *KCNQ1* gene adequately explain the clinical phenotype: the reduced potassium extrusion capabilities of the mutant IKs channels impair the repolarization process, leading to a prolongation of cellular action potential and of QT interval that produces an electrically unstable substrate predisposing to the development of ventricular tachycardia and fibrillation.

Interestingly, mutations of the *KCNQ1* and *KCNE1* genes that lead to a "gain of function" represented by an increased IKs repolarizing current have been identified in patients affected by a disease called the "short QT syndrome" (SQTS) and in patients affected by familial atrial fibrillation (FAF). In the presence of gain of function mutation and of an excess of potassium repolarizing current, the cardiac action potential and refractory period shortens in the atria and in the ventricles, facilitating reentrant arrhythmias[6] (see Table 25–1).

Fast Delayed Rectifier (IK_r) Current and Associated Phenotypes

KCNH2 and *KCNE2* genes encode the α-(HERG) and the β-(MiRP) subunits of the potassium channel conducting the IK_r current, the rapid component of the cardiac delayed rectifier. The *KCNH2*-encoded protein, HERG, is a six-transmembrane segment protein that forms homotetramers in the plasmalemma to make up functional channels. The

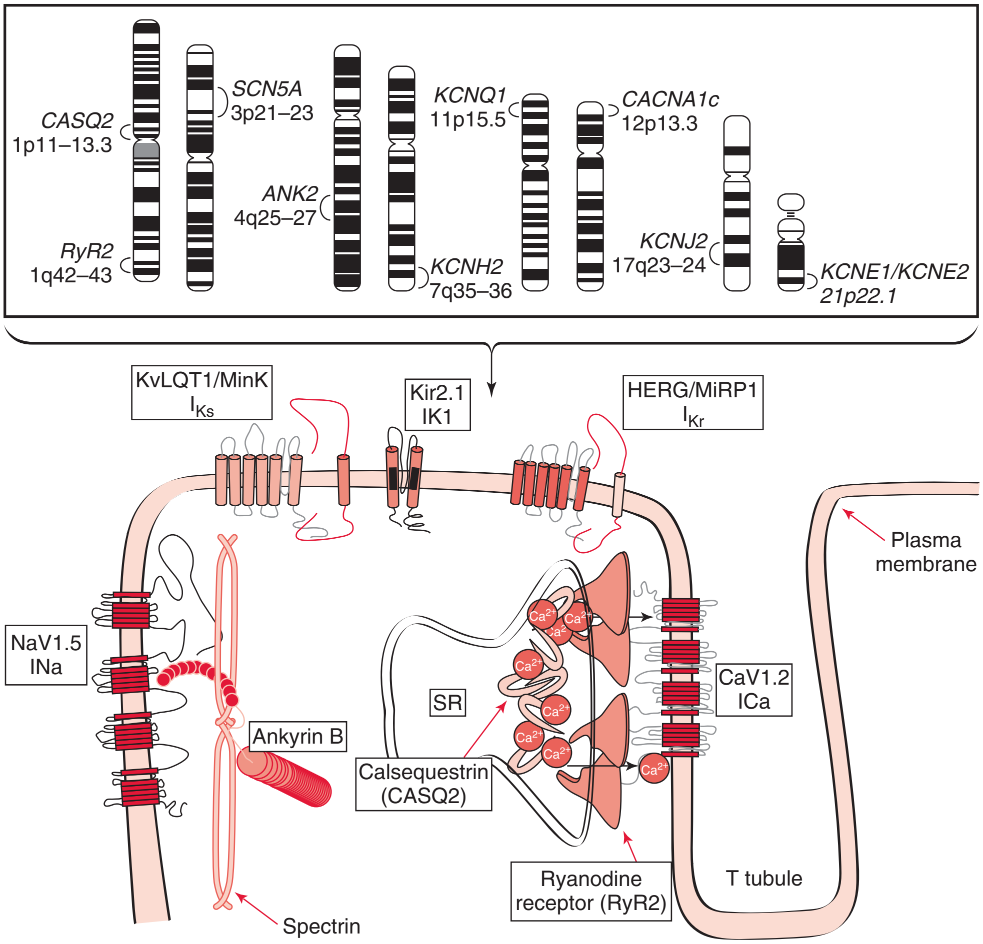

Figure 25–1 Genes and proteins involved in inherited arrhythmias. The *upper panel* shows symbols and chromosomal localization of the genes involved in inherited arrhythmogenic disorders. The proteins encoded by these genes (plasmalemmal and sarcoplasmic reticulum [SR] channels, and intracellular proteins) are schematically illustrated in the *lower panel.*

physiologic role of MIRP protein to recapitulate the current has been postulated,[7] although coassembly of MIRP with other voltage-gated potassium channels such as KvLQT1 has been also reported.[8]

Loss of function mutations in *KCNH2* and *KCNE2* cause the LQT2 and LQT6 variants of the long QT syndrome (see Table 25–1). Although LQT2 is the second most common variant of LQTS and accounts for 35% to 40% of mutations (http://www.fsm.it/cardmoc), mutations in the *KCNE2* gene[7] are uncommon (<1%) and are associated with mild clinical manifestations. *KCNH2* mutations found in LQTS patients cause a reduction of IK_r current (loss of function).[4] Gain of function *KCNH2* mutations causing an increased IK_r have been reported in patients with SQTS,[9] whereas the *KCNE2* mutation that causes an arginine-to-cysteine mutation at position 27 (R27C) has been reported in familial atrial fibrillation (FAF).[8] This latter mutation was found in 2/28 probands of families with FAF in whom a systematic screening of cardiac ion channel encoding genes was carried out. Functional study revealed that the mutation had a gain-of-function effect on the *KCNQ1-KCNE2* channel; unlike long QT syndrome-associated *KCNE2* mutations, it did not alter *KCNH2–KCNE2* current.

Inward Rectifier (IK1) Current and Associated Phenotypes

The inwardly rectifying potassium channels (Kir2.x) primarily mediate cardiac IK1. The Kir family includes two transmembrane segment channels that coassemble in the membrane by forming homo- or heterotetramers.[10] IK1 current plays an important role in late-phase repolarization and in maintaining the resting membrane potential. Among known Kir-encoding genes, only the *KCNJ2* encoding for the Kir2.1 has been associated with genetically determined cardiac arrhythmias[11,12](http://www.fsm.it/cardmoc).

KCNJ2 mutations were initially identified in patients with Andersen-Tawil syndrome,[11] a multisystem disease characterized by potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. Patients with Andersen syndrome present with a variable degree of QT interval prolongation and, therefore, this disorder is also referred to as LQT7. Additional *KCNJ2* mutations have been identified in families with SQTS and FAF.[12,13] Analogous to what has been previously described for mutations in IKr and IKs proteins, *KCNJ2* mutations also lead to different phenotypes because they may cause either a gain of function or a loss of function. As expected from the electrocardiographic phenotype, mutations identified in patients with LQT7 cause a loss of function, whereas those identified in patients with SQTS and FAF mutations produce a gain of function (see Table 25–1).

Overall, experimental data demonstrate that three major repolarizing currents are involved in the pathogenesis of inherited arrhythmogenic syndromes (IKs, IKr, and IK1). At the cellular level, all of them may harbor both loss and gain of function mutations, and the associated clinical phenotypes vary accordingly. These findings highlight the remarkable genetic and phenotypic diversity of inherited arrhythmias.

Table 25–1 Potassium Channels Involved in Inherited Arrhythmias

Gene	Protein	Phenotypes	Mechanism	Inheritance
KCNQ1	I_{Ks} potassium channel α-subunit (KvLQT1)	Long QT syndrome (LQT1, JLN1) Short QT syndrome (SQTS2) Familial atrial fibrillation	Loss of function Gain of function Gain of function	AD/AR AD
KCNH2	I_{Kr} potassium channel α-subunit (HERG)	Long QT syndrome (LQT2) Short QT syndrome (SQTS1)	Loss of function Gain of function	AD
KCNE1	I_{Ks} potassium channel β-subunit (MinK)	Long QT syndrome (LQT5, JLN2)	Loss of function	AD/AR
KCNE2	I_K potassium channel β-subunit (MiRP)	Long QT syndrome (LQT6)	Loss of function	AD
KCNJ2	I_{K1} potassium channel (Kir2.1)	Long QT, potassium-sensitive paralysis, dysmorphic features (LQT7—Andersen syndrome) Short QT syndrome (SQTS3)	Loss of function Gain of function	AD AD

AD,autosomal dominant; AR; autosomal recessive; JLN, Jervell and Lange-Nielsen syndrome.

Sodium Current (INa)

The cardiac sodium channel (Nav1.5), encoded by the *SCN5A* gene, is a transmembrane protein composed of four homologous domains (DI-DIV), each containing six transmembrane spanning segments (S1 to S6). Thus, unlike potassium channels, there is no need for coassembly of subunits to obtain a pore-forming protein.

Four arrhythmogenic disorders have been linked to *SCN5A* mutations. Three of them have an autosomal dominant pattern of inheritance (the LQT3 variant of long QT syndrome,[14] the Brugada syndrome [BrS],[15] the progressive cardiac conduction defect [CCD],[16] and the fourth is inherited as autosomal recessive sick sinus syndrome [SSS]) (Table 25–2).

SCN5A-related phenotypes are due to either gain (LQT3) or loss (BrS, CCD, SSS) of function mutations. It is still unclear why some loss of function mutations of the *SCN5A* gene cause CCD, whereas others cause BrS: it is, therefore, possible that the phenotype is the result of variable expressivity of a single disease that may manifest either with ST-segment elevation in the right precordial leads or with conduction abnormalities. The understanding of what mediates the prevailing phenotypic manifestation is still unclear.

Calcium Current (ICa) and Intracellular Calcium Handling

Calcium entry through plasmalemmal voltage-gated channels (ICa current) is the major determinant of the duration of the plateau of the cardiac action potential. The presence of a normal Ca^{2+} inward current is critical to ensure the rapid mobilization of Ca^{2+} from the sarcoplasmic reticulum stores, which trigger the contractile protein activation—the so-called "calcium-induced-calcium release" (CICR) (see Fig. 25–1).

Since 2001, molecular genetic studies have linked mutations in key proteins responsible for the regulation of intracellular calcium with two forms of inherited arrhythmias, namely the Timothy syndrome and the catecholaminergic polymorphic ventricular tachycardia (Table 25–3).

Timothy syndrome (TS), also called LQT8, is a severe variant of long QT syndrome presenting with QT interval prolongation and cutaneous syndactyly of the hands and feet. In a study by Splawski and colleagues,[17] a missense mutation in the *CACNA1c* gene, encoding for the L-type calcium channel (Cav1.2), has been identified with 13 TS probands. Interestingly, all patients presented with the same single amino acid substitution (G403R), and all but one (a case of parental mosaicism), were sporadic cases. Heterologously expressed Cav1.2-G403R mutant channels resulted in an almost complete loss of voltage dependency of channel inactivation with a consequent increase of calcium inward current. Therefore, the net effect of the Timothy syndrome defect is that of a gain of function of the calcium channel causing, at cardiac level, an increased action potential duration.[17] Until now, there was no disease associated with loss of function mutations of the *CACNA1c* gene.

Another key element in the CICR process is the control of Ca^{2+} release from sarcoplasmic reticulum in response to calcium entry from the extracellular space during the plateau phase of action potential. Several proteins are involved in this process and two of them have been associated with the autosomal dominant and autosomal recessive variant of catecholaminergic polymorphic ventricular tachycardia (CPVT).[18] In late 2000, we demonstrated that the cardiac ryanodine receptor gene (*RyR2*), encoding for the sarcoplasmic reticulum (SR) Ca^{2+} releasing channel,[19] causes the autosomal dominant CPVT. The role of this gene was subsequently confirmed by others.[20,21] A few months later, Lahat and coworkers[22] provided the evidence linking *CASQ2*, the cardiac calsequestrin gene, to the autosomal recessive variant of CPVT. *CASQ2* serves as a major Ca^{2+} binding protein localized in the terminal cisternae of the SR and cooperates with the control of the calcium release process from the SR. In vitro expression studies of mutant RyR2 are in agreement by indicating that

Table 25–2 Sodium Channel–Associated Phenotypes

Gene	Protein	Phenotypes	Mechanism	Inheritance
SCN5A	I_{Na} Cardiac sodium channel α-subunit (Nav 1.5)	Long QT syndrome (LQT3)	Gain of function	AD
		Brugada syndrome (BrS1)	Loss of function	AD
		Progressive cardiac conduction defect (CCD1)	Loss of function	AD
		Sick sinus syndrome (SSS)	Loss of function	AR

AD,autosomal dominant; AR = autosomal recessive.

Table 25–3 Calcium Handling Abnormalities in Cardiac Arrhythmias

CACNA1C	I_{Ca} Voltage-gated calcium channel, CaV1.2	Timothy syndrome (LQT8), long QT with syndactyly, septal defect, patent foramen ovale, mental retardation	Gain of function	Sporadic/parental mosaicism
RyR2	Cardiac ryanodine receptor	Catecholaminergic polymorphic ventricular tachycardia (CPVT1)	Gain of function	AD
CASQ2	Calsequestrin	Catecholaminergic polymorphic ventricular tachycardia (CPVT2)	Loss of function	AR

AD,autosomal dominant; AR, autosomal recessive.

the RyR2 mutations cause a Ca^{2+} “leakage” from the SR in condition of sympathetic (catecholamines) activation.[23-25] The authors have developed a knock-in RyR2 mutant mouse that presents the typical CPVT arrhythmias,[26] thus supporting the role of triggered activity as the cellular mechanism of arrhythmias.

One experimental study showed that a defective calsequestrin impairs the SR Ca^{2+} storing and release functions via a reduced Ca^{2+} buffering capability and suggested that, similar to *RyR2*-related CPVT, triggered activity is the cellular arrhythmogenic mechanism.[27]

Inherited arrhythmogenic diseases were initially believed to involve only the plasmalemmal ion channels. The identification of RyR2 and CASQ2 mutations in CPVT provided the evidences that even intracellular proteins may cause abnormal cardiac excitability in a structurally normal heart. Another example is represented by the LQT4 variant of LQTS recently linked to the *ANK2* gene.[28] *ANK2* encodes for an intracellular protein (Ankyrin) that regulates the proper intracellular localization of plasmalemmal ion channels (calcium channel, sodium channel, sodium/calcium exchanger), sarcoplasmic reticulum channels (ryanodine receptor, inositol triphosphate receptor), and other adhesion molecules.[28] From a clinical standpoint, LQT4 is an uncommon condition characterized by QT interval prolongation, sinus bradycardia, paroxysmal atrial fibrillation with polyphasic T waves—but the few cases reported so far do not allow a detailed description of the ANK2-related phenotype.

Taken as a whole, the available data depict the complexity of the pathways underlying inherited arrhythmogenic diseases (Fig. 25–2). Although the common denominator of these diseases is vulnerability to malignant ventricular arrhythmias and sudden death in young subjects with a structurally intact heart, they differ profoundly in terms of pathogenesis and clinical phenotype. The evidence that all the plasmalemmal channels so far associated with inherited arrhythmias may harbor both gain and loss of function mutations further substantiates this concept.

PHENOTYPES, CLINICAL PRESENTATION, AND MANAGEMENT

Although molecular genetics has unveiled the pathogenesis of several inherited arrhythmia syndromes, with the exception of LQTS, there is still a knowledge gap preventing the full applicability of genetics to clinical management. This gap is mainly due to the lack of large cohorts of patients with known mutations that allow genotype-based risk stratification and therapy. In the following paragraphs, we will summarize the main phenotypic features of the most important inherited arrhythmogenic diseases, and we will outline the relevance of genetic to clinical management.

Long QT Syndrome

Clinical Presentation and Its Modulation by Genotype

The long QT syndrome (LQTS) is characterized by a variable degree of QT interval prolongation and an increased susceptibility to life-threatening ventricular arrhythmias in the absence of structural abnormalities of the heart. The mean age at onset of symptoms (syncope or sudden death) is 12 years, and an earlier onset of clinical manifestations is an indicator of adverse prognosis.[29] The diagnosis of LQTS is ECG-based: the measurement of the QT interval corrected for heart rate and the morphology of the ST-T wave must be taken into consideration. Because QT interval is modulated by gender, differential limits must be considered after puberty: QTc should not exceed 440 msec in males and 460 msec in females.[30]

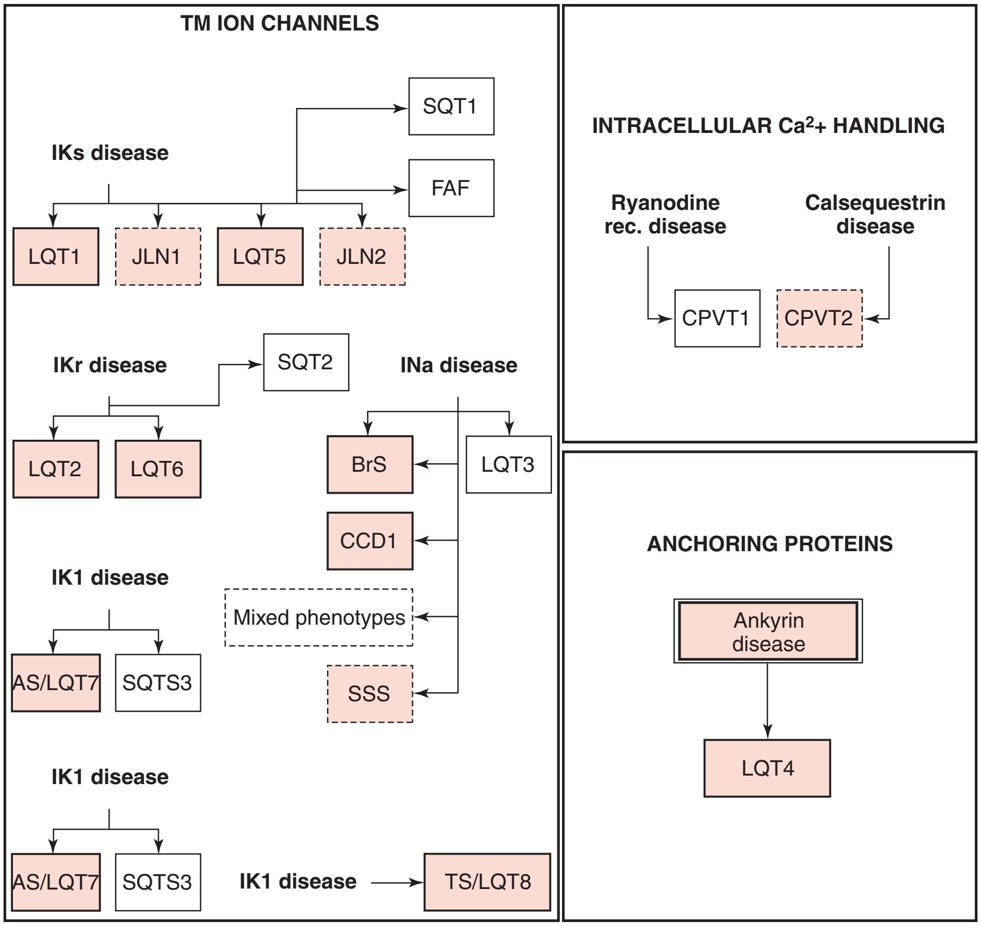

Figure 25–2 Classification of inherited arrhythmogenic diseases according to functional pathways. Three major classes of proteins are identified: transmembrane (TM) ion channels, intracellular calcium handling proteins, and anchoring proteins. *Light pink rectangles* represent diseases caused by loss of function mutations, whereas *white rectangles* represent gain of function mutations. *Continuous lines* and *dotted lines* depict autosomal dominant and autosomal recessive disorders, respectively. "Mixed phenotypes" (e.g., BrS + LQT) are caused by complex biophysical abnormalities of sodium current (INa) (http://www.fsm.it/cardmoc). For abbreviations, see text and tables. (Modified by Priori SG: Inherited arrhythmogenic diseases: The complexity beyond monogenic disorders. Circ Res 2004;94:140-5.)

QTc assessment is the most important step for the diagnosis of LQTS; however, morphologic ST-T wave abnormalities are often evident in LQTS and may support the clinical diagnosis. Further insights into the morphology of ST-T pattern in LQTS may be obtained when the ECG presentation is considered in light of the genetic background. Indeed, the distinguishing of genotype-specific repolarization patterns has been reported.[31,32] Albeit not a surrogate for genetic testing, the morphologic ECG evaluation may be important in defining the genotyping strategy with an advantage to the turnaround time of the analysis (Fig. 25–3).

The onset of rapid polymorphic VT (torsades de pointes) underlies syncope in LQTS.[33] According to the genetic substrate, the triggering factors for cardiac events may vary: LQT1 patients have 90% of lethal events during physical or emotional stress; LQT2 patients are at higher risk for lethal events during arousal or emotional stimulation (49%); LQT3 patients present most of their events (64%) at rest or while asleep and only 4% during exercise.[34] Furthermore, swimming-related events are frequent among LQT1, whereas an acoustic stimulus is a specific trigger for LQT2.[35,36]

Natural History and Risk Stratification

Developments in molecular genetics have allowed the integration of traditional clinical variables (electrocardiographic evaluation, personal, and family history of cardiac events) with the genotype information to reach clinically applicable risk stratification schemes based on natural history. Molecular epidemiology studies[37-39] show that LQT1, LQT2, and LQT3 variants account for approximately 95% of genotyped patients, whereas the other variants are infrequent (<5%). Thus, genotype-phenotype correlations have been carried out mainly on these three subtypes.

Evaluation of the natural history of LQTS on a very large group of patients with known genotype was carried out in 2003 by Priori and colleagues in a cohort of 647 LQTS patients from 193 families.[40] By combining QTc distribution and genotype, it was shown that among LQT1 and LQT2 patients, those with a QTc in the upper quartile (>500 msec) had a 5.3- and 8.4-fold risk increase, respectively, compared with those in the first quartile. However, LQT1 showed a lower cumulative event-free survival versus LQT2 and LQT3.[40] Gender had a different effect across genotypes. It had no influence among LQT1 patients, whereas a higher risk was present for LQT2 females and LQT3 males. It was also observed that the percentage of genetically affected patients with a normal QT interval ("silent mutation carriers") differed strikingly among genotypes, being much more frequent ($P < 0.001$) among LQT1 (36%) than LQT2 (19%) and LQT3 (10%).

In smaller patient groups, it has been suggested that risk stratification may be further refined when the location of a mutation is also taken into consideration. In 2002, Moss and colleagues[41] studied 201 LQT2 patients and showed that individuals with mutations in the pore region were at greater risk

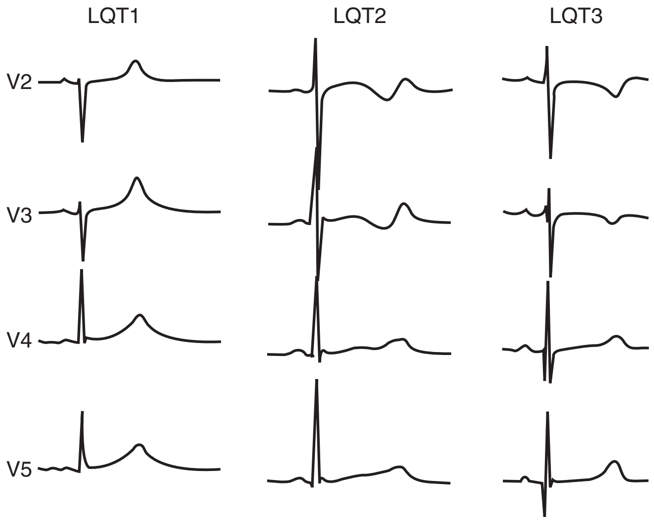

Figure 25–3 Genotype-specific T wave morphology in long QT syndrome (LQTS). Examples of typical precordial lead (V_2-V_5) repolarization morphologies in LQTS patients. From *left to right*: LQT1 smooth broad-based T wave, LQT2 biphasic and notched T wave with low amplitude, LQT3 straight ST-segment with smooth but narrow T wave.

for cardiac events than patients with non-pore mutations—even though the difference was not significant for lethal events (aborted cardiac arrest and sudden death). Some authors suggested that mutations located in the carboxy terminus of the *KCNQ1* gene were associated with a mild clinical phenotype, but these data were not confirmed thereafter.[42,43] Overall, data concerning localization-specific risk stratification require further investigation before reaching a full clinical applicability.

Therapy

The mainstay of LQTS therapy is administration of a β-blocker,[44] which is indicated for all patients with clinically overt LQTS—with or without a history of syncope. An implantable cardioverter-defibrillator (ICD) plus β-blockade is indicated for secondary prevention in patients with an aborted cardiac arrest and for those experiencing a recurrent cardiac event on therapy.[45]

In a study carried out in LQTS patients with known genotype, we demonstrated that genotype has a significant influence on the effectiveness of therapy.[29] Indeed β-blockers are significantly more effective among LQT1 as compared with LQT2 patients (HR versus LQT1 2.81; 95% CI: 1.50 to 5.27) and LQT3 patients (HR versus LQT1 4.00; 95% CI: 2.45 to 8.03). Besides genotype, additional independent predictors of recurrence of cardiac events on therapy were the presence of a first cardiac event before therapy in early childhood (≤7 years) and a QTc interval >500 msec. These data suggest that LQT2 and LQT3 patients with a QTc interval >500 msec are at high risk of events despite active β-blocker therapy. For these individuals, ICD implantation could be considered for primary prevention.

A further clinically relevant issue that progressively emerged after the discovery of LQTS genes is that of silent mutation carriers. These individuals, who represent approximately 30% of all genotyped LQTS patients, despite a normal QT interval, still present a 10% risk for cardiac events before age 40.[40] Thus, the use of prophylactic therapy with β-blockers should be considered for these individuals.

Role of Genetic Testing

The screening of the five LQTS genes (*KCNQ1, KCNE1, KCNE2, KCNH2, SCN5A)* allows identification of the genetic defect in 60% to 70%[37,39,46] of clinically affected individuals. However, because not all the genes for LQTS have been discovered, the lack of identification of a genetic defect cannot rule out the presence of the disease. Screening of family members of a genotyped proband allows presymptomatic diagnosis and it allows definition of the clinical status (affected versus nonaffected) in borderline cases.

Of major relevance, and somewhat unique to LQTS, is the fact that the identification of the genetic defect contributes to risk stratification, therapy selection, and prevention of factors that precipitate arrhythmias (Table 25–4). Indeed, the most recent genotype-phenotype correlation data[29] show that β-blockers provide satisfactory protection against cardiac events among LQT1 patients (*KCNQ1* mutations), whereas LQT2 and LQT3 (*KCNH2* and *SCN5A* mutations, respectively) retain a significant risk of cardiac events (23% among LQT2 and 32% among LQT3). This study also demonstrated that genotype is an independent predictor of events on therapy together with the QT interval duration and the occurrence of a first event in early childhood (≤7 years).[29] Thus, prophylactic ICD implantation was suggested for LQT2 and LQT3 patients with QTc > 500 msec and a history of early events. These data clearly underscore the relevance of genotyping in LQTS. The development of novel strategies to make genetic testing widely available is, therefore, strongly advisable.[46]

Short QT Syndrome

Clinical Presentation and Natural History

The short QT syndrome is a new clinical entity that is associated with sudden cardiac death, syncope, and/or atrial fibrillation. The first report of a clinical condition characterized by abnormally short repolarization was made by Gussak and associates in 2000.[47] They described two siblings and their mother who displayed persistently short QT interval (260 to 275 msec) and a peculiar hyperkalemic-like T wave pattern on the resting ECG. A few additional unrelated cases (<20) were reported thereafter.[6]

As with the majority of inherited arrhythmogenic diseases, SQTS is also characterized by the absence of structural heart disease and by family history of sudden cardiac death in approximately 40% of cases.[6] The available data suggest an overall high mortality rate in the absence of a specific trigger for cardiac events. It should be noted, however, that the very first families affected by a newly described disease tend to have the more malignant form of the condition and this may lead to an overestimation of the severity of the disease. Therefore, it may still be too early to draw conclusions on the incidence of sudden cardiac death in patients with the diagnosis of SQTS. The low number of patients so far reported also prevents the definition of prevalence and genotype-phenotype correlation.

Table 25–4 Indication for Genetic Testing in Inherited Arrhythmogenic Diseases

	LQTS	LQTS-TS*	LQTS-AS*	BrS	SQTS	FAF	CCD	SSS	CPVT
Success rate (%)†	65-70	100	>50	20-25	?	?	?	?	65-70
Presymptomatic diagnosis	X	X	X	X	X	X	X	X	X
Identification of silent carriers	X	**	X	X	X	X	X	X	X
Risk stratification	X								
Therapy	X		X						
Lifestyle modification	X		X	X					X
Reproductive counseling	X	X	X	X	X	X	X	X	X

*The two LQTS variants with extracardiac involvement have been listed separately because applicability of genetic testing is different.
† percentage of successfully genotyped probands with clinically overt phenotype.
**No silent carriers have been reported with the exception of one case of parental mosaicism.
BrS, Brugada syndrome; CCD, cardiac conduction defect; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; LQTS-TS, long QT syndrome 8 (LQT8) Timothy syndrome; LQTS-AS, long QT syndrome 7 (LQT7) Andersen syndrome; SQTS, short QT syndrome; SSS, sick sinus syndrome.

An important, still-debated issue in SQTS is the QT cut-off limit to establish the diagnosis. The initial patients reported by Gussak[47] had a QT interval of 260 to 275 msec. In 2003, Gaita and associates,[48] reported two families with SQTS and showed that all affected patients had a QTc < 300 msec with a QT interval <280 msec. However, we reported a novel form of short QT syndrome in patients with a QTc up to 320 msec long.[12] The observation obtained in the long QT syndrome showed a sizeable overlap of QTc values between normal individuals and genetically affected patients with normal QTc (approximately 30% of all LQTS), and also put forward the idea that the same overlap could happen at the lower QTc boundary zone between normal and SQTS patients. We extrapolate from these data that SQTS cannot be excluded in patients with a QTc or a QT between 300 to 320 msec.

Therapy

No effective treatment has been identified so far, and the lack of robust markers of risk may suggest the use of ICD for both secondary and primary prevention of sudden cardiac death. However, careful device programming is needed because inappropriate ICD discharges due to T wave oversensing have been reported.[6,49]

Based on the evidence that SQTS is caused by an excess of outward repolarizing current, the use of potassium channel blockers has been considered. Specifically, attempts have been made to counteract the effect of *KCNH2* mutations using sotalol, ibutilide, and quinidine.[50] Only this latter compound was effective in prolonging the QT-interval in the small group of SQTS patients who received this therapy. Indeed, Brugada and colleagues[9] demonstrated that the SQTS-*KCNH2* defect reduces the affinity of a more specific IKr blocker such as sotalol for the mutant channel.

Role of Genetic Testing

Three genes associated with SQTS have been brought to light in only a 5-year time span, but the clinical applicability of genetic testing is still limited. Only a handful of families has been genotyped; therefore, the relative prevalence of the three variants and the genotype-phenotype correlation is still unknown. Thus, the usefulness of genetic testing is still limited, although it is advisable for early diagnosis of asymptomatic individuals owing to the malignancy of the disease (see Table 25–4).

Brugada Syndrome

Clinical Presentation

Brugada syndrome (BrS) is clinically characterized by peculiar ECG alterations (ST-segment elevation in leads V_1–V_3 and complete or incomplete right bundle branch block) and risk of sudden cardiac death due to the onset of fast polymorphic VT and ventricular fibrillation.[51,52] Although a high prevalence of sporadic cases may be seen in clinical practice, BrS is inherited as an autosomal dominant trait.

Diagnosis of BrS may be complicated by the transitory nature of the ECG abnormalities.[53-56] Provocative testing with intravenous administration of sodium channel blockers (flecainide 2 mg/kg or ajmaline 1 mg/kg) (Fig. 25–4), may help to unmask the ECG abnormalities in suspected cases,[57,58] but its sensitivity is yet undefined.[59] The morphology of ST elevation in BrS has also been a matter of debate in the last few years, and criteria have been modified over time. In the earlier reports, BrS diagnosis was considered in the presence of both a "coved-type" and a "saddle-back" ECG pattern.[60] Subsequently,[52] only coved-type ECG (either spontaneous or pharmacologically induced) has been reported as diagnostic for the disease (see Fig. 25–4). In 2005, more restrictive criteria were introduced in a consensus document[61] in which the presence of a coved-type ECG was not considered sufficient for diagnosis in the absence of additional criteria—such as programmed electrical stimulation (PES) inducibility and ventricular arrhythmias (syncope or cardiac arrest). However, this definition is called into question by the results of genetic analysis that shows that carriers of loss-of-function mutation may have a saddle-back ECG and may remain asymptomatic or may not be inducible at PES.[59]

Natural History Risk Stratification and Therapy

Clinical manifestations of BrS include syncope and cardiac arrest—typically occurring in the third and fourth decades of

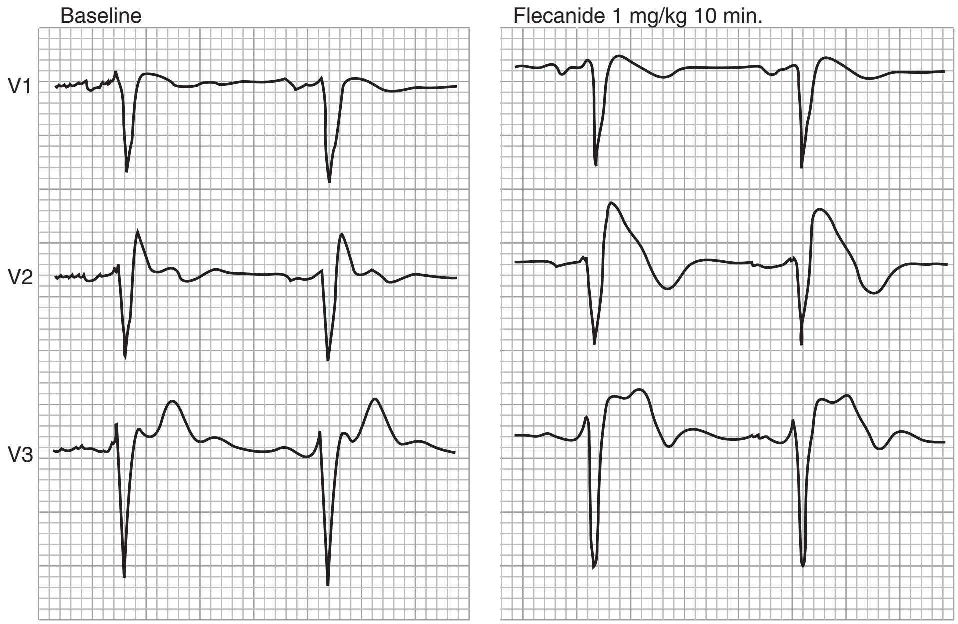

Figure 25–4 ECG in Brugada syndrome (BrS). Right precordial leads V_1-V_3 in a patient with Brugada syndrome recorded at baseline and after pharmacologic challenge with intravenous flecainide. At baseline, (*right panel*) incomplete right bundle branch block and ST elevation (more clearly visible in V_3) with a "saddle-back" morphology are evident. After drug administration, ST elevation is increased >2 mm with conversion to a "coved-type" morphology.

life, and usually at rest or during sleep. Despite the initial reports suggesting a very high incidence of lethal events,[62] it is now evident that most BrS patients are likely to remain asymptomatic.[63-66] The overall picture suggests that approximately 20% of BrS patients have at least one cardiac event in a lifetime. Because an effective pharmacologic therapy has not yet been identified and because the only effective strategy to prevent sudden death is ICD implantation, the risk stratification becomes a primary issue for clinical management.

Although the use of an ICD for secondary prevention of an aborted cardiac arrest is clearly indicated, the correct strategy for identification of patients in whom an ICD is indicated for primary prevention is still debated. The decision should be based on a reliable quantification of risk. In 2002, we showed that the presence of a spontaneous ST-segment elevation in leads V_1, V_2, and/or V_3, especially when associated with a history of syncope, was one of the most robust indicators of risk of cardiac events.[64] This concept was subsequently confirmed by other investigators.[65] On the other hand, the ICD indications for asymptomatic patients remain controversial. This group of patients has a relatively low risk of cardiac events. We reported that 14% of patients experienced a life-threatening event from birth to age 40,[64] and this picture has been more recently confirmed by other authors who reported an 11% aborted sudden death rate in 212 patients with a mean age at diagnosis of 44 years.[67] Therefore, the induction of ventricular fibrillation at PES has been proposed as a risk stratification tool.[65] Unfortunately, short- and long-term reproducibility of PES is unsatisfactory[68,69]; the number needed to treat (NNT = 20) for the use of ICD is high[59]; and the data from an Italian[64] study and from a German[67] study did not confirm the conclusion of Brugada and associates[65] on the good predictive value of PES. Overall, these data do not support the use of PES for risk stratification of asymptomatic Brugada patients, leaving open the issue of identifying a more robust risk stratification marker for this subgroup of patients.

Oral quinidine has been proposed as a gene-specific therapy for BrS patients on the hypothesis that it could reduce the transmural dispersion of ventricular repolarization.[70] Available clinical data show that quinidine prevents arrhythmia inducibility at PES in up to 76% of BrS patients[71-73] and suggest a positive long-term effect in preventing the occurrence of spontaneous arrhythmias.[72] Unfortunately, a high incidence of GI side effects may reduce patient compliance (see Chapter 21).[71] These data are clearly insufficient to propose quinidine as a routine BrS treatment. Nonetheless, this drug should be considered to reduce the number of ICD discharges in highly symptomatic patients with frequent recurrences.

Role of Genetic Testing

Only the *SCN5A* gene has been so far associated with the BrS and only 15% to 20% of patients harbor mutations in this gene.[63] Because the disease manifests in adulthood and it is characterized by incomplete penetrance (i.e., presence of mutation carriers without clinical phenotype),[63,64] the value of genetic analysis for reproductive counseling is less obvious than in other genetic arrhythmias. Genetic analysis is useful in nonpenetrant mutation carriers and in family members of genotyped probands to monitor them to detect early signs of manifestation of the disease but, at present, it is not useful for risk stratification (see Table 25–4).[59]

Progressive Conduction Defects and "Overlapping Syndromes"

Clinical Presentation and Natural History

Cardiac conduction defect (CCD) represents the major cause for pacemaker implantation in the world and one of the more common disorders of the heart. The disease is usually progressive and it is characterized by a slowing of electrical conduction through the His-Purkinje system, which may manifest at the surface ECG with a prolongation of the PR interval and a QRS widening. Complete atrioventricular block may occur with the possible consequence of syncope and sudden death. In some instances, progressive CCD is associated

with other cardiac (e.g., dilated cardiomyopathy) and extracardiac (e.g., muscular dystrophy) manifestations.

Familial cases of isolated progressive CCD with an autosomal dominant pattern of transmission have been reported, and linkage studies have outlined a disease locus on chromosome 19 (19q13.2-q13.3). No gene has been identified so far at this locus,[74] but in 1999 Schott and coworkers[16] reported mutations in the *SCN5A* gene that segregate with CCD in an autosomal dominant fashion in two families. This finding demonstrated that a loss of function mutation in a transmembrane ion channel may be responsible for a defect of impulse conduction in the heart. Additional mutations have been reported thereafter by other groups (http://www.fsm.it/cardmoc). Interestingly, some CCD-*SCN5A* mutations may also cause more complex phenotypes that overlap with the Brugada syndrome and LQT3.[4] Despite the fact that such findings are relevant to understanding the pathophysiology of some CCD cases, the natural history, response to therapy, and risk stratification schemes are still poorly characterized owing to the low number of patients genotyped so far.

Role of Genetic Testing

The yield of *SCN5A* screening in CCD patients is still unknown; therefore, genetic testing is useful for presymptomatic diagnosis and reproductive risk assessment but not for risk stratification and therapy (see Table 25–4).

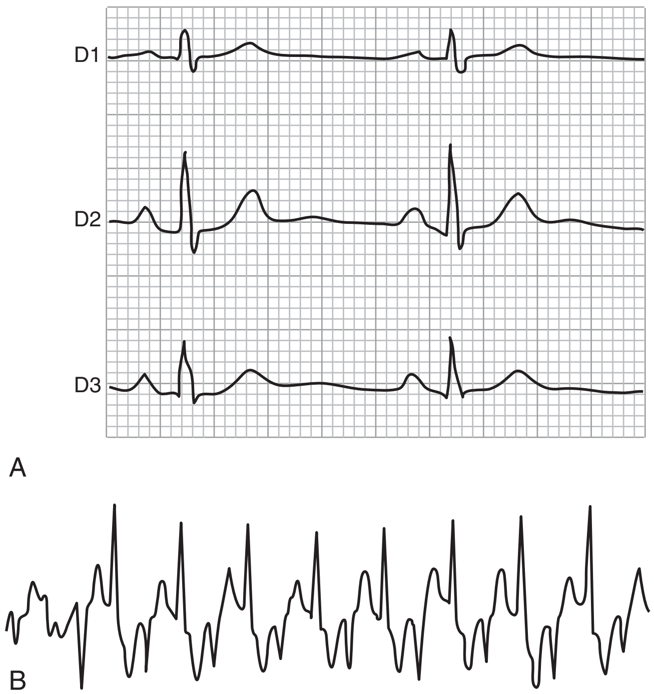

Figure 25–5 ECG in catecholaminergic polymorphic ventricular tachycardia (CPVT). **A,** shows limb leads (D1-D3) of a CPVT patient. No major abnormalities may be observed. The same patient during exercise stress test (**B**) developed the typical pattern of bidirectional ventricular tachycardia with positive and negative QRS complexes alternating on a beat-to-beat basis.

Catecholaminergic Polymorphic Ventricular Tachycardia

Clinical Presentation

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an arrhythmic disorder that is clinically characterized by ventricular tachycardia, syncope, and sudden death—occurring in familial as well as in sporadic cases.[75] Three distinguishing features are also present[75] (1) direct relationship between adrenergic activation (physical or emotional stress) and cardiac events; (2) typical pattern of bidirectional ventricular tachycardia (VT), with an unremarkable resting electrocardiogram (Fig. 25–5); and (3) a structurally normal heart.

Physical activity or acute emotions are the specific triggers for arrhythmias among CPVT patients. The onset of ventricular arrhythmias is typically reproducible in term of onset heart rate (120 to 130 beats per min) and morphology (alternating 180-degree QRS axis on a beat-to-beat basis—the so-called “bidirectional ventricular tachycardia”). In some instances, however, polymorphic VT without a “stable” QRS vector alternans may be observed.[21,76]

Natural History and Risk Stratification

CPVT usually manifests with syncope triggered by exercise or acute emotion, although sudden cardiac death may be the first manifestation in some families.[21] Symptoms often manifest during childhood with a mean age at first event of 8 years, and approximately 30% of families present with a history of one or multiple premature sudden deaths that usually occur during childhood even if later events also occur (after age 20).[21,77] CPVT is a severe clinical condition, as outlined by data from our registry, including the largest cohort of CPVT patient available: in the absence of appropriate therapy >70% of patient experience syncope or aborted cardiac arrest before the age of 40 years.[78]

The amount of clinical and genetic data so far available does not allow drawing robust genotype-phenotype correlations and risk stratification algorithms. CPVT patients are usually not inducible at PES, making it inadequate for management and risk stratification.[21,77] Preliminary evidence shows that patients with RyR2 mutation have events at a younger age than do patients with nongenotyped CPVT and that male sex is a risk factor for syncope in *RyR2*-CPVT (relative risk = 4.2).[21] The clinical presentation of *CASQ2*- and *RyR2*-related CPVT is similar, although it has been suggested that *CASQ2*-CPVT most often manifests with polymorphic instead of bidirectional ventricular tachycardia.[22,79]

Therapy

Antiadrenergic treatment with β-blockers (in our clinic patients are most often given nadolol 1.5 to 2.5 mg/kg/day) is the cornerstone of therapy for CPVT patients.[21,77,80] The reproducible pattern of arrhythmia during exercise stress test among CPVT patients allows dose titration and monitoring. Chronic treatment can prevent recurrences of syncope in many patients,[21,77] although for approximately 40% of them, the arrhythmia control is unsatisfactory. In such instances, the use of an ICD is indicated because the available evidence

shows appropriate interventions of the device in one half of the implanted patients—despite the antiadrenergic therapy.[21]

Role of Genetic Testing

The screening of the two genes (*RyR2* and *CASQ2*) associated with the autosomal dominant and autosomal recessive forms of CPVT allows the identification of mutations in 70% of patients.[18,78] Even if only two genes are responsible for most of the CPVT cases, genetic analysis of this disease is complicated by the fact that *RyR2* is one of the largest genes in the human genome. Turnaround time and test availability are still, therefore, far from ideal. However, because the clinical diagnosis of CPVT is fairly elusive and because the ECG is unremarkable, genetic analysis may become extremely helpful for establishing the diagnosis. This is especially important because CPVT is a highly malignant disease if left untreated. On the contrary, once it is diagnosed and the appropriate treatment is implemented, the patient's prognosis improves substantially. Presymptomatic diagnosis, diagnosis in silent carriers, and reproductive counseling are additional important benefits of successful genetic analysis (see Table 25–4).

CONCLUSIONS

Transmembrane and intracellular ion channels and transporters have been implicated in cardiac arrhythmias and sudden death. Molecular genetics has revealed a high level of genetic and functional heterogeneity, and the same protein may generate a variety of apparently unrelated (sometimes opposite) clinical phenotypes depending on the specific functional consequences of the single mutations (see Fig. 25–2). Despite such complexity, our understanding of cardiac physiology and pathophysiology has improved substantially in the last decade. Translation into clinical benefits is, again, a complex process that has only recently achieved partial success with progressively more informative management algorithms derived from genotype-phenotype correlations. In the years to come, this process will lead to the development of individualized approaches for prevention and therapy of cardiac arrhythmias and sudden death.

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Dyslipoproteinemias/ Atherosclerosis

Chapter 26

Pharmacologic Therapy for Hypertriglyceridemia and Low HDL: Rationale for Combination Therapy

Michael H. Davidson

CHAPTER CONTENTS

Statin outcome trials have proven conclusively that lowering low-density lipoprotein cholesterol (LDL-C) results in significant improvement in the rate of cardiovascular morbidity or mortality. Additionally, primary and secondary prevention studies using statins have established the safety and efficacy of this class of pharmacologic agents. The relationship between LDL-C and coronary heart disease (CHD) events appears to be linear with considerable evidence supporting the "lower is better" hypothesis. However, even with low LDL levels, the residual risk for subsets of high-risk patients continues to be elevated. In the Treating to New Targets (TNT) trial, patients on atorvastatin 80 mg (with a mean LDL-C of 77 mg/dL) had a total of 28% cardiovascular events compared with a 33% event rate for patients on 10 mg atorvastatin with mean LDL-C of 101 mg/dL (a 22% relative risk reduction).[1] Therefore, approximately 70% of the events were not avoided despite significant LDL-C reduction. The 80-mg atorvastatin therapy was also associated with a slightly elevated rate of increased transaminases (0.2% versus 1.2%).[1] Therefore, an important clinical challenge remains to reduce further the residual CHD risk on optimal statin therapy without adversely affecting patient safety.

HIGH-RISK SUBSETS OF PATIENTS FOR CHD EVENTS ON STATIN THERAPY

Posthoc and prespecified analyses of statin outcome trials demonstrate higher CHD event rates for patients with additional risk factors. Of the modifiable risk factors, the presence of diabetes, cigarette smoking, metabolic syndrome, and elevated hs-CRP predicts a high residual risk. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) Guidelines update regarding the implication of recent clinical trials recommends an optional LDL-C goal of <70 mg/dL and a non-HDL goal of <100 mg/dL for patients at very high risk.[2] The definition of very high risk included patients with cardiovascular disease with diabetes, cigarette smoking, or factors associated with the metabolic syndrome (Table 26–1). A contemporary survey documented that 75% of patients with cardiovascular disease (CVD) would meet this definition of "very high risk."[3] Therefore pragmatically, most patients with CVD should be considered appropriate for the optional LDL goal of <70 mg/dL. In the Heart Protection Study (HPS) statin therapy (simvastatin 40 mg daily) resulted in highly significant reductions in coronary mortality rate

(18%), incidence rate of first nonfatal myocardial infarction (38%), stroke incidence (25%), and incidence of coronary revascularization (30%),[4] but the diabetic patients with CHD on statin therapy had an event rate of 31% compared with a placebo event rate of 25% in nondiabetic patients with CHD (Table 26–2). In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, intensive (atorvastatin 80 mg/dL) compared with moderate (pravastatin 40 mg/dL) lipid lowering resulted in greater reductions in LDL-C to mean levels of 78.9 mg/dL compared with 110.4 mg/dL, respectively ($P < 0.001$). In addition, the intensive lipid-lowering intervention resulted in a significantly lower progression rate in the percentage change in atheroma volume ($P = 0.02$).[5] However, the diabetic subset on aggressive lipid-lowering therapy of atorvastatin 80 mg continued to have marked progression of atheroma volume. In the ARBITER 2 trials, the diabetic subset also continued to have progression of IMT despite statin therapy.[6]

A review of diabetic patients or patients with low HDL in statin event trials demonstrates a markedly elevated rate of residual events even on statin treatment (see Table 26–2). In fact, the on-statin event rate in patients with diabetes or low HDL is higher than the placebo event rate for patients without diabetes or low HDL. Therefore, even with an LDL-C <70 mg/dL, a CVD patient with diabetes is likely to have a high recurrent event rate. In the HPS trial the subgroup of patients with low HDL had a significant benefit from simvastatin therapy. CHD events decreased from 29.9% to 22.6%, but the patients on statin therapy still had a higher event rate than the placebo patients in the subgroup with a higher HDL.[4] A similar relationship exists for patients in the HPS trial with elevated triglyceride (TG) levels. Because hs-CRP correlates with the metabolic syndrome, an elevated hs-CRP (>2 mg/L) may represent an important marker of enhanced residual risk. This chapter reviews the use of nonstatin therapies to modify the CHD risk associated with dyslipidemia and the use of combination therapy to reduce the residual risk for patients on statin monotherapy.

Table 26–1 Updated NCEP/ATP III Guidelines

Risk Category	LDL-C Goal
Very high risk defined as: Cardiovascular disease and one or more of: 1) Diabetes mellitus 2) Multiple major risk factors 3 Poorly controlled risk factors 4) Metabolic syndrome 5) Patients with acute coronary syndrome	<100 optional <70
High risk: CHD or CHD risk equivalent	<100
Moderately high risk: • 2 or more risk factors • Framingham score 10-20%	<130 Optional <100
Moderate risk: • 2 or more risk factors • Framingham score <10%	<130
Low risk 0-1 risk factors	<160

CHD, coronary heart disease.

NIACIN

Niacin or nicotinic acid is a soluble B vitamin that has favorable effects on all major lipid subfractions (Table 26–3)[7] but has not been widely used due to the side effect profile. Despite the significant lipid-altering effects, pharmaceutical data in the United States have consistently documented that niacin prescriptions are less than 3% of the very large cholesterol drug market. In Europe the use of niacin is even lower than in the United States. However, clinical trial data suggest a potential important role for niacin therapy, and the FDA has approved a modified release form of niacin (Niaspan) that reduces the side effect profile.

Table 26–2 Event Rates in Statin Trials

	Without Diabetes		With Diabetes	
	On Statin	On Placebo	On Statin	On Placebo
HPS* (CHD patients)	19.8%	25.7%	33.4%	37.8%
CARE*	19.6%	24.6%	28.7%	36.8%
LIPID†	11.7%	15.2%	19.7%	22.8%
PROSPER†	13.1%	16%	23.1%	18.4%
ASCOT†	4.9%	8.7%	9.6%	11.4%
	High HDL on Statin	High HDL on Placebo	Low HDL on Statin	Low HDL on Placebo
HPS*	17%	20.9%	22.0%	29.9%
CARE/LIPID*	18.5%	22.4%	25%	30.8%
PROSPER†	12.8%	11.6%	13%	19.3%

*Coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), unstable angina.
†CHD death and non-fatal MI.
ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CARE, Cholesterol and Recurrent Events; HDL, high-density lipoprotein; HPS, Heart Protection Study; LIPID, Long-Term Prevention with Pravastatin in Ischaemic Disease; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk.

The pharmacokinetics of niacin and its mechanism of action are not well understood, but niacin appears to reduce apolipoprotein (apo) B secretion, thereby lowering both very low-density lipoprotein (VLDL) and LDL and increasing apo AI and lowering Lp(a).[8] Niacin reduces the mobilization of free fatty acids from the periphery probably by inhibiting hormone sensitive lipase. Therefore, there is less TG substrate for VLDL synthesis and a reduced secretion of VLDL, which is the precursor of LDL (Fig. 26–1). Niacin may also inhibit diacylglycerol-2-acyltransferase (DGAT), a key enzyme in TG synthesis. On average, niacin lowers LDL by 10% to 20%, TGs by 20% to 40%, and Lp(a) by 10% to 30%, and it raises HDL by 15% to 30%.[9] These effects are dose related and shown in Figure 26–2. Niacin is the only known approved lipid-altering drug (with the exception of estrogen) that lowers Lp(a) and is the most potent drug used to raise HDL. Niacin appears to increase HDL by decreasing the hepatic uptake of Apo AI, thereby delaying catabolism.[10] HDL can be taken up by hepatocytes by at least two cellular receptors. SRB1 binds HDL, and cholesteryl ester is effluxed into the hepatocytes. This receptor is not affected by niacin but rather another mechanism of hepatocyte uptake of HDL that most likely involves holouptake of the entire HDL particle. Holouptake of HDL would remove the lipoprotein from circulation; after SRB1 uptake, the delipidated HDL is released to resume reverse cholesterol transport. By inhibiting the holouptake rather than SRB1, niacin promotes cholesteryl ester removal from HDL that results in a longer circulating time for HDL and theoretically improves reverse cholesterol transport.[11]

Niacin can cause significant hepatotoxicity and should be discontinued if liver enzymes (SGOT and SGPT) exceed 3 times the upper limit of normal. Patients who use over-the-counter (nonprescription) niacin should be worried about the hazard of liver toxicity.[12] Many over-the-counter niacin supplements may not be labeled as sustained release, but if niacin is combined with a fiber, such as oat or rice bran, this combination can cause a sustained release and adversely affect the liver enzymes. Patients should generally be advised not to use over-the-counter niacin. Niacin can also increase uric acid levels, thus aggravating gout. Other side effects of niacin include a rash, gastrointestinal problems including worsening of esophageal reflux or peptic ulcers and headache. Rarely, skin lesions, usually in the axillary areas or elbows, called *acanthosis nigricans* can develop.

Niacin is often added to a statin in patients with combined hyperlipidemia, especially if the HDL is low or Lp(a) is high. A number of studies have evaluated the combination of a statin with niacin.[13] The incidence of liver function abnormalities with the combination of a statin plus niacin is generally similar to niacin therapy alone, at least when the combination of both drugs are at the starting doses (e.g., simvastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg plus niacin 1500 to 2000 mg/d). Myopathy has been reported with statins plus niacin, but the incidence appears to be less than expected with gemfibrozil.[14] Myopathy has developed with the combination, after niacin-induced hepatotoxicity reduces the catabolism of the statin, resulting in markedly elevated statin levels. Therefore, unregulated sustained release niacins that have a higher incidence of hepatotoxicity should be avoided in combination therapy. The vast majority of combination trials have used either immediate-release niacin or sustained release niacin. In one study a single tablet containing both modified-release niacin and lovastatin was dose titrated from niacin 500 mg plus lovastatin 10 mg to niacin 2000 mg plus lovastatin 40 mg to target levels based on NCEP guidelines over a 16-week period.[15] Once on a stable dose, the patients were followed further for 36 weeks. More than 600 patients were enrolled with LDL levels exceeding the NCEP ATP II levels for

Table 26–3 Effects of Niacin

Niacin Decreases	Niacin Increases
Total cholesterol	HDL cholesterol
Total triglycerides	HDL_2 cholesterol
VLDL-C	HDL_3 cholesterol (<HDL_2)
LDL-C	Apolipoproteins A-I, A-II
Small dense LDL	LP A-I
Lp(a)	LP A-I + A-II (<LP A-I)
Apo B	LDL particle size
Total cholesterol/HDL-C	
LDL-C/HDL-C	
Apo B/A-I	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

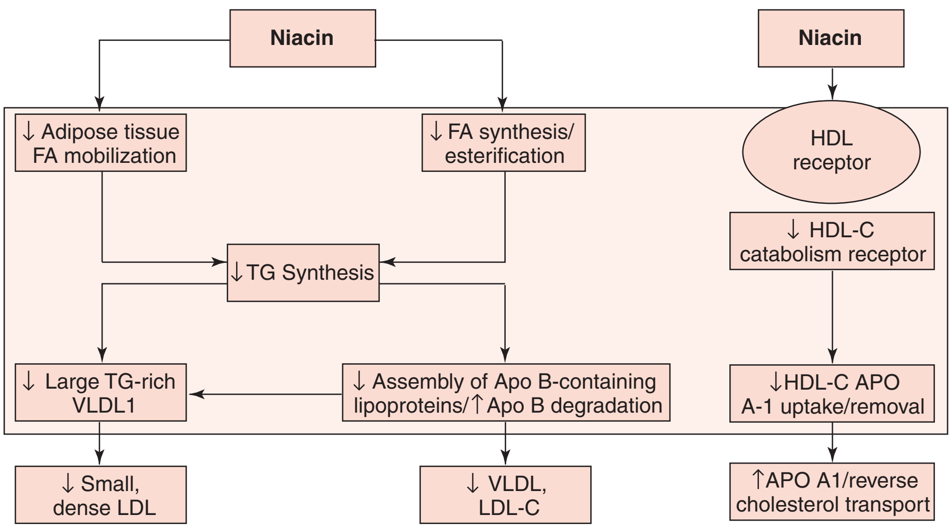
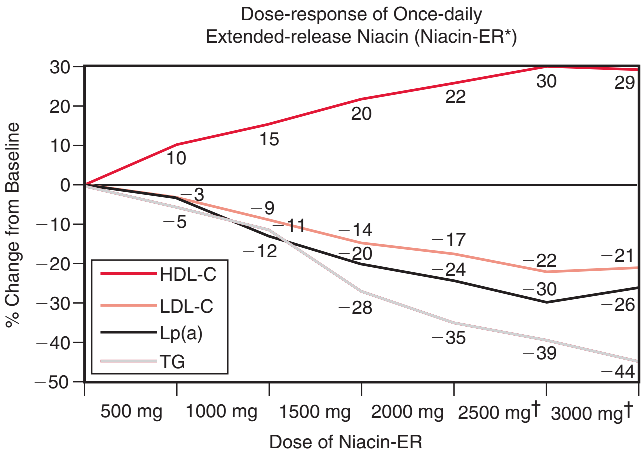


Figure 26–1 Actions of niacin in treating dyslipoproteinemias.

initiating drug therapy. At the 2000/40 mg dose LDL was lowered by 47% and TGs by 42%, and HDL increased by 30%. About 7% of patients withdrew as a result of flushing. There were no cases of drug-induced myopathy, and less than 1% had elevated liver enzymes greater than 3 times the upper limit of normal.

Due to the safety data of Niaspan in combination with a statin, there has been a resurgence of interest in the use of combination therapy to maximize risk reduction in patients with dyslipidemia.[16] Over the past several years, statins have established a large clinical trial base documenting both safety and outcome benefits. Niacin also has demonstrated CHD outcome benefits either as monotherapy or in combination with other lipid-lowering agents (Table 26–4).[17-22] The marked reduction in clinical events in the FATS and HATS trials, although relatively small trials, has provided intriguing data regarding the importance of combining niacin with other lipid-lowering agents. Statins, in general, have demonstrated approximately a 30% reduction in CHD events, but in these small trials when a statin was combined with niacin, the reduction in CHD events was approximately 75%. This 75% reduction in clinical events by combining a statin with niacin is far more expected than with LDL reduction alone. This marked reduction in CHD events suggests that the other effects of niacin, such as raising HDL and lowering TGs and Lp(a), contribute significantly to the benefits. Although the clinical benefit of changing the LDL particle size from small (pattern B) to large (pattern A) is not yet conclusively demonstrated, niacin is one of the most effective agents in modifying LDL particle size, whereas statins are more effective in lowering the total LDL particle numbers.[23,24]



*Niaspan
†Greater than recommended daily doses

Figure 26–2 Dose-response of once-daily extended-release niacin (Niacin-ER). (Redrawn from Goldberg AC: Clinical trial experience with extended-release niacin [Niaspan]: Dose-escalation study. Am J Cardiol 82(12A):35U-38U, 1998.)

A subanalysis of the HATS trial showed that statin-niacin therapy significantly increased the large Apo A-1 containing α-1 HDL particles.[25] This increase in the larger HDL particles was associated with less progression of coronary stenosis even after adjusting for traditional risk factors.[25] Although statins may also increase larger HDL levels, niacin appears to have the most significant effect on the levels of the large LpA-1 particles. These data suggest that niacin was a significant contributor to the benefits of the simvastatin-niacin combination treatment in the regression of atherosclerotic development and CHD event reduction.

By recommending non-HDL, as well as LDL, targets if the TGs exceed 200 mg/dL, the ATP III guidelines have also enhanced the need for niacin therapy.[26] On the basis of an evaluation of the safety and pharmacokinetics of statins in combination with fibrates or niacin, an algorithm was developed to use appropriate combination treatment if non-HDL goals have not been achieved (Fig. 26–3).[14]

The use of niacin in diabetics has in the past been considered problematic due to niacin's modest glucose-raising effects. A trial and a reevaluation of the Coronary Drug Project (CDP)[27,28] have provided helpful information on the use of niacin in patients with glucose elevations. A reevaluation of the CDP in the diabetic subpopulation had a similar

Table 26–4 Niacin Coronary Heart Disease Endpoint Trials

Study	Population	Results
Coronary Drug Project	8341 post-MI men Baseline TC 250 mg/dL—9.9% on trial Baseline TG 177 mg/dL—26.1% on trial	27% reduction in definite non-fatal MI—24% reduction in CVA. Total mortality decrease 10.6% at 15 yrs.
Stockholm Ischemia Heart Study	555 consecutive MI survivors <70 yrs old; open label clofibrate/niacin or placebo; baseline TC 245 mg/dL—13% on trial Baseline TG 208 mg/dL—19% on trial	36% reduction in CHD deaths.
Familial Atherosclerosis Treatment Study	146 men with APO B ≥125 mg/dL with CHD. Conventional therapy versus niacin/colestipol or lovastatin/colestipol.	73% reduction in CHD events in patients who received intensive lipid-lowering therapy.
HDL Atherosclerosis Treatment Study (HATS)	160 CHD patients with HDL <35 mg/dL, LDL <145 mg/dL. Treated 3 yrs with niacin/simvastatin or placebo with or without antioxidants.	Reduction of CHD events by 60% (on antioxidants) to 90% (off antioxidants).

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; MI, myocardial infarction.

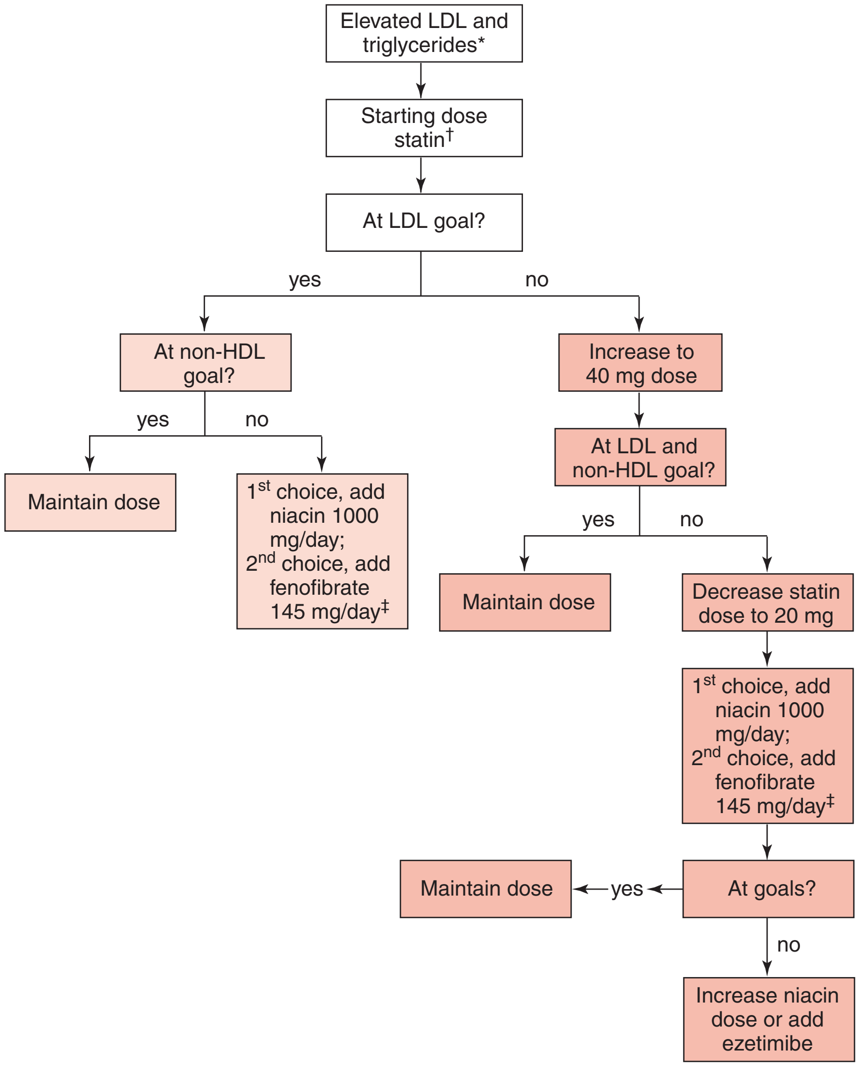


Figure 26–3 Algorithm to maximize safety of lipid-lowering therapy. *At baseline, check LFT, CPK, thyroid profile; document presence of muscle soreness, tenderness, or pain. †Food and Drug Administration-approved starting dose statins: lovastatin, 20 mg, 40 mg; simvastatin, 10, 20, 40 mg; atorvastatin, 10, 20, 40 mg; fluvastatin, 20, 40, 80 mg XL; pravastatin, 10, 20, 40 mg. ‡Consider low-dose statin plus ezetimibe for patients at high risk for statin-induced myopathy.

reduction in clinical CHD events than did the nondiabetic CHD population. This new information provides support for the use of niacin to treat diabetic dyslipidemia, and although there may be a modest increase in serum glucose levels, the overall benefit is a marked reduction in cardiovascular events. In the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT),[29] 148 patients with type 2 diabetes and dyslipidemia were randomized to 1000 mg/d, 1500 mg/d of sustained release niacin or placebo; 47% of the patients were also taking statins.

In the ADVENT trials, extended-release niacin produced a significant effect on both TGs and HDL-C levels. The increase in HDL-C was dose dependent and was significantly greater at all time points for the niacin-treated groups than for the placebo group. In the 1000 mg niacin group, HDL-C increased up to 19% at 16 weeks. In the 1500 mg group, it increased up to 24%. The absolute increases in HDL-C at 16 weeks were 7.6 mg/dL in the 1000 mg group and 11 mg/dL in the 155 mg group, compared with 1.6 mg/dL among placebo-treated patients.

TG reductions were also dose related. Reductions in the patients who received lower-dose niacin were not significantly greater than for those who received placebos. TG levels were reduced by 28% in the 1500 mg niacin group at 16 weeks, a significant difference compared with placebo.

Changes in Hb A_{1c} levels were small in all treatment groups. Hb A_{1c} values in the 100 mg/d treatment group were not significantly different from the placebo group. Changes in Hb A_{1c} levels in the 1500 mg/d group reached marginal significance ($P = 0.048$) at 16 weeks. Increases in fasting blood glucose occurred between weeks 4 and 8 in the niacin-treated groups; levels returned to baseline by week 16.

The ADVENT study demonstrated that extended-release niacin, at the doses tested, is effective and well tolerated in patients who have type 2 diabetes and atherogenic dyslipidemia, whether given alone or with a statin. Low doses of extended-release niacin are therefore an option for the treatment of dyslipidemia in patients who have glucose-controlled type 2 diabetes.

Because of demographic trends toward more obesity and diabetes, the ATP III requirement to treat non-HDL goals, as well as LDL goals, in hypertriglyceridemic patients will become more difficult. Niacin provides a unique range of benefits to the lipid profile that is difficult to achieve with statin therapy alone in many patients. In clinical trials in which both statins and niacin were used together, there have

been impressive reductions in CHD events, although these trials have been relatively small. New information regarding the use of niacin in diabetics has moved this therapy from a relative contraindication to the use of niacin with the appropriate monitoring of glucose levels.

FIBRATES

Five fibrates are currently used in human therapy: clofibrate, gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate. Only gemfibrozil and fenofibrate are available in the United States. Fibrates are peroxisome proliferator-activated receptor (PPAR-alpha) ligands. PPAR-alpha activated by fibrates forms heterodimers with the 9-*cis* retinoic acid receptor (RXR). The PPAR/RXR heterodimers bind to peroxisome proliferator response elements, upregulating the expression of these genes. PPAR-alpha activation by fibrates leads to increasing lipoprotein lipase expression and decreasing apo CIII expression, which results in enhanced catabolism of TG-rich particles. Fibrates also increase the expression of apo AI and apo AII.[30] The net result of fibrate therapy is decreased hypertriglyceridemia and an increase in HDL cholesterol. LDL levels may also decrease, most likely due to a reduction of dense LDL, which is more atherogenic than buoyant LDL and has poor affinity for the LDL receptor. However, LDL may also increase in patients with hypertriglyceridemia with fibrate therapy, but these are usually the less atherogenic buoyant LDL particles. Consequently, fibrates are used almost exclusively for patients with hypertriglyceridemia and low HDL.

Several outcome trials have used fibrates. In patients with hypertriglyceridemia or low HDL, or both, these drugs reduce CHD events or the angiographic progression of atherosclerosis (Table 26–5). In patients with CHD and low HDL, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study[31] shows that gemfibrozil compares favorably with statin therapy, using a number needed to treat (NNT) to prevent one event analysis. The BIP trial failed to demonstrate a significant overall benefit, but for patients with TGs greater than 200 mg per dL, there was a 40% CHD risk reduction ($P = 0.03$).[32] The mean LDL in the VA-HIT study was 111 mg per dL compared with 148 mg per dL in the BIP trial. The lack of benefit for bezafibrate in the BIP trial compared with the significant benefit for gemfibrozil in the VA-HIT study suggests that fibrates need to be targeted for patients with either high TGs or low HDL with a relatively low LDL.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial[33] did not reduce nonfatal and fatal myocardial interactions significantly (11% reduction, $P = 0.16$), but a secondary endpoint that included fatal CVD events (nonfatal, fatal myocardial interactions, coronary revascularization, and stroke) was reduced significantly by 11% ($P = 0.035$). This study was compromised by a higher statin drop-in rate in the control group during the treatment period, which resulted in only minimal changes in the lipid profile between the two groups. The FIELD patients with preexisting CHD (≈20% of the study patients) had the highest statin drop-in rate during the study, and if the diabetics without CHD (≈80% of the study patients) are evaluated posthoc, there is a 25% CHD reduction, which is comparable with statin trials with diabetic patients.

FIBRATE SIDE EFFECTS AND SAFETY ISSUES

The fibrates are generally well tolerated. The most common side effects are upper gastrointestinal disturbance, headache, myalgia, and loss of libido.[34] Fibrates have absolute contraindications in hepatic or severe renal dysfunction and preexisting gallbladder disease. Fibrates should also not be used in pregnant or nursing mothers.

Gemfibrozil is a potent inhibitor of the cytochrome P450 2C8 metabolic pathway and the glucuronidation of statins.[35] Cerivastatin is partially cleared by the CYP 2C8 pathway and

Table 26–5 Fibrate Outcome Studies

Trial	Duration Yrs	N	Treatment	Primary Endpoint	RRR	ARR	NNT
Primary Prevention							
HHS	5	4081	Gemfibrozil 600 mg bid	Fatal, nonfatal MI and cardiac death	34%	1.4%	71
FIELD	5	9795	Fenofibrate 200 mg	Fatal and nonfatal MI	11%	1.3%	77
FIELD Subgroup without CVD	5	7664	Fenofibrate 200 mg	Total MI cardiovascular events	19%	2.0%	50
Secondary Prevention							
BIP	6.2	3090	Bezafibrate 400 mg qd	Fatal, nonfatal MI, sudden death	9% (NS)	NA	NA
BIP subgroup TG >200	6.2	459	Bezafibrate 400 mg qd	Fatal, nonfatal MI, sudden death	39%	7.7%	13
VA-HIT	5.1	2531	Gemfibrozil 1200 mg qd	Nonfatal MI and CHD death	22%	4.4%	23

APR, absolute risk reduction; BIP, bezafibrate infarction prevention study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HHS, Helsinki Heart Study; MI, myocardial infarction; N, number of participants; NNT, number needed to treat; RRR, relative risk reduction; VA-HIT, Veterans Affairs High Density Lipoprotein Intervention Trial.

undergoes significant glucuronidation. Gemfibrozil's inhibitory effect on both metabolic pathways for cerivastatin explains the fivefold to sixfold increase in the area under the curve (AUC) for cerivastatin when combined with gemfibrozil.[36] Fenofibrate, which does not inhibit the CYP 2C8 metabolic pathway or statin glucuronidation, has a minimal impact on cerivastatin levels. All statins including rosuvastatin require varying degrees of glucuronidation for metabolism, and the AUC for all statins evaluated, except for fluvastatin, are increased when combined with gemfibrozil (Table 26–6). This explains gemfibrozil's greater propensity to increase the risk of rhabdomyolysis when combined with statins, as compared with fenofibrate.[37]

CYP 2C8 is a common metabolic pathway for many of the diabetic treatments, such as glimepiride, rosiglitazone, and repaglinide. Gemfibrozil, as an inhibitor of the CYP 2C8 metabolic pathway, raises the AUC for all these drugs significantly. Therefore, gemfibrozil should only be used rarely in combination with CYP 2C8 metabolized drugs.[38,39] Alternatively, fenofibrate can be used as a substitute for gemfibrozil without adversely affecting the AUC of CYP 2C8 metabolized drugs.

Although gemfibrozil and fenofibrate are both fibrates and activate PPAR-alpha, resulting in similar lipoprotein changes (fenofibrate may more potently decrease LDL), these drugs have very different pharmacokinetic profiles. Gemfibrozil is a competitive inhibitor of the cytochrome P450 2C8 metabolic pathway, organic anion transport protein 2 (OATP2), and statin glucuronidation.[40] Fenofibrate is a substrate for the cytochrome P450 2C9 metabolic pathway but is not an inhibitor and is also a mild inhibitor of P-glycoproteins. These metabolic pathways appear to result in little known drug interactions for fenofibrate. The gemfibrozil-statin interaction is most problematic because a fibrate is frequently necessary to add to a statin to improve the lipoprotein profile. Both fenofibrate and, perhaps less commonly, gemfibrozil may rarely increase serum creatinine by an unknown mechanism. The most likely explanation appears to relate to increases in creatinine production in muscle tissue, but renal filtration changes are also possible. The homocysteine level is increased by both fenofibrate and gemfibrozil. Although the clinical significance of increased homocysteine level with fibrate therapy is uncertain, on the basis of a correlation between increased homocysteine levels and CHD risk and the demonstrated benefit of folic acid supplementation as a means of decreasing the fenofibrate-associated increase in homocysteine, it appears prudent to consider folic acid supplementation for

Table 26–6 Statin/Fibrate Combination Therapy: Pharmacokinetic Interactions

	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	No effect
Simvastatin	↑ in C_{max} by 2-fold	No effect
Pravastatin	↑ in C_{max} by 2-fold	No effect
Rosuvastatin	↑ in C_{max} by 2-fold	No effect
Fluvastatin	No effect	No effect
Lovastatin	↑ in C_{max} by 2.8-fold	No effect
Cerivastatin	↑ in C_{max} by 2.3-fold	No effect

C_{max}, maximum concentration.

patients on fibrate therapy.[41] Both fenofibrate and gemfibrozil lower the fibrinogen level, but neither fibrate significantly alters Lp(a) level.

Gemfibrozil is usually dosed at 1200 mg at two divided doses 30 minutes before the morning and evening meals. Micronized fenofibrate, 145 mg, is given with a meal. The pharmacokinetic profile of micronized fenofibrate is markedly affected by food, and unless a patient takes the capsule with a meal, its absorption may be suboptimal. A new formulation of micronized fenofibrate is available that does not require intake with food and therefore should improve patient compliance. The recommended dose of bezafibrate is 400 g once daily as a sustained-release tablet, and ciprofibrate is given at 100 g daily.

CLINICAL SIGNIFICANCE OF NONSTATIN PLEIOTROPIC EFFECTS

Nonstatin therapies also have a multitude of potential pleiotropic effects. Niacin lowers Lp(a) and fibrinogen while increasing HDL and modifying LDL particle size. Ezetimibe lowers plant sterol levels and alters the cholesterol composition of postprandial chylomicrons. Both bile acid sequestrants and ezetimibe may affect FXR (bile acid receptor) or LXR (oxysterol receptor), or both, by altering bile salts/biliary cholesterol absorption.

As PPAR-alpha agonists, fibrates affect the expression of numerous genes that alter lipoprotein metabolism or the development of atherosclerosis (Fig. 26–4). PPAR-alpha agonism upregulates the genes involved in reverse cholesterol transport. Fenofibrate has been shown to upregulate macrophage ABCA1, which increases efflux of free cholesterol into nascent HDL[42] and enhances the uptake of HDL by the hepatic SRBI receptors, which results in increased biliary cholesterol excretion. PPAR-alpha agonists also appear to have numerous anti-inflammatory and antithrombotic effects that may reduce plaque rupture vulnerability to induce clinical events (Fig. 26–5). Although the clinical benefits of these pleiotropic effects of nonstatin therapies remain speculative, intriguing posthoc analyses from fibrate trials support additional clinical benefits of PPAR-alpha agonism in patients with metabolic syndrome or diabetes. In the fibrate outcomes trials, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[43] and the Helsinki Heart Study (HHS),[44] the subset of patients with diabetes had a greater risk reduction than did the patients without diabetes (Fig. 26–6). In the VA-HIT trial[43] the occurrence of a new cardiovascular event and the benefit of fibrate therapy were much less dependent on levels of HDL-C or TGs than on the presence or absence of insulin resistance.

RATIONALE OF COMBINATION THERAPY

In light of the residual risk of CHD events in statin trials within certain subgroups, combination therapy appears most appropriate in patients with a high rate of events despite optimal statin treatment. These subgroups include patients with LDL-C levels >70 mg/dL, diabetics, those with metabolic syndrome, those with elevated hs-CRP, and cigarette smokers.

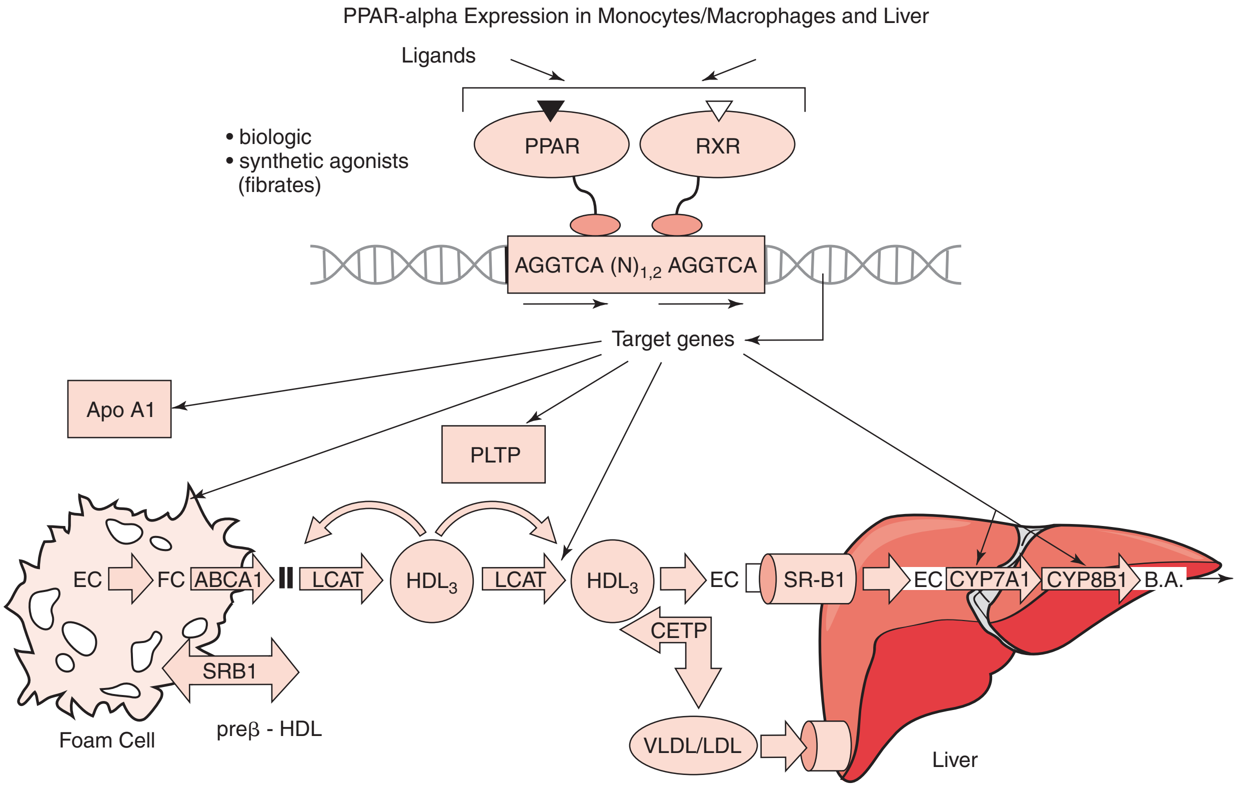


Figure 26–4 PPAR-alpha expression in monocytes/macrophages and liver.

A survey demonstrated that 75% of patients with CVD met the definition of "very high risk" according to the NCEP ATP III update report.[3] In this survey only 18% of patients at "very high risk" had an LDL <70 mg/dL and only 4% had an LDL <70 mg/dL and a non-HDL <100 mg/dL if TGs were >200 mg/dL. These data support the use of more aggressive statin therapy and the implementation of combination therapy as needed to achieve these optional targets in the "very high risk" patient population.

Although further LDL-C lowering may provide additional clinical benefits to patients with diabetes or metabolic syndrome, or both, the posthoc analysis of clinical trials has

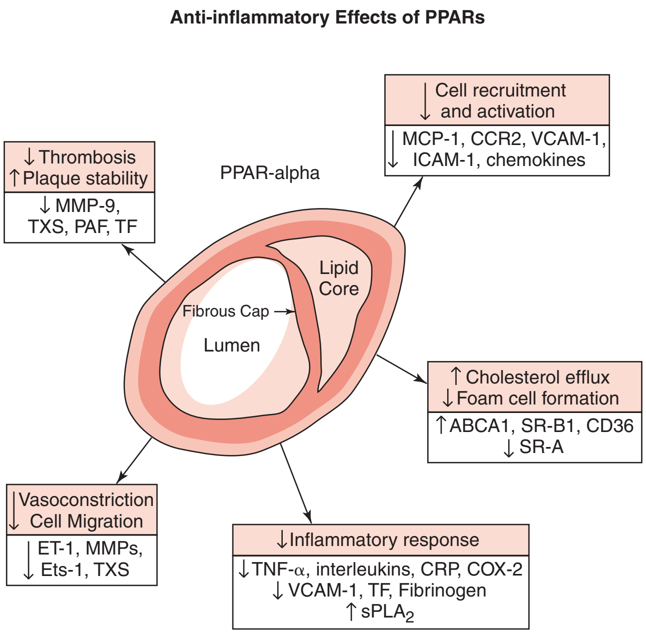


Figure 26–5 Anti-inflammatory effects of PPARs.

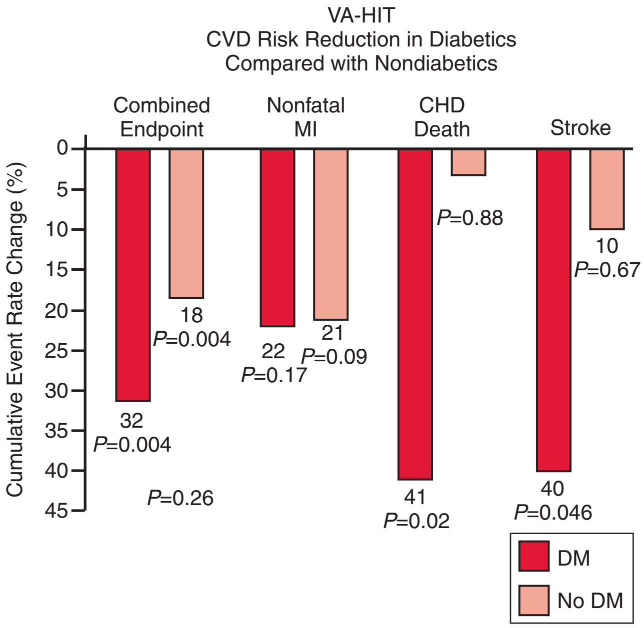


Figure 26–6 CVD risk reduction in diabetics compared with nondiabetics in Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT).

demonstrated a very high residual risk even with low LDL-C levels. Surrogate endpoint trials also demonstrate significant atherosclerotic progression in diabetics on statins or on a combination of statins and niacin. Because fibrates appear to have unique benefits in patients with insulin resistance, the combination of a statin and a fibrate is potentially most appropriate in this patient population. The Action to Control Cardiovascular Risk in Diabetes (ACCORD)[45] trial is testing this hypothesis in approximately 10,000 diabetics on simvastatin randomized to fenofibrate or placebo to evaluate CHD outcomes.

The additive effects of simvastatin and fenofibrate on lipid parameter have been documented in the Simvastatin Plus Fenofibrate for Combined Hyperlipidemia (SAFARI) trial.[46] Simvastatin monotherapy (20 mg/d) was compared with combination therapy (simvastatin 20 mg/d plus fenofibrate 160 mg/d) in patients with combined hyperlipidemia (fasting TG levels >150 and <500 mg/dL and LDL-C >130 mg/dL). Mean LDL-C levels decreased significantly with combination therapy compared with monotherapy (31.2% and 25.8%, respectively, $P < 0.001$). In addition, mean HDL-C levels significantly increased with combination therapy compared with monotherapy (18.6% and 9.7%, respectively, $P < 0.001$) and no drug-related serious adverse events occurred.[46]

THE SAFETY OF COMBINATION THERAPY

Although combination therapy is widely used and, in fact, recommended by expert panels for the management of hypertension and diabetes, combination treatment of dyslipidemia is seldom clinically applied in practice. In the National Cholesterol Education Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE)[3] survey, only 5% of patients on treatment were on combination therapies. The major reason combination therapy has not been widely used in practice is the perception of adverse safety associated with combining a statin with niacin or a fibrate. In the labeling for all statins are cautionary notes regarding the combination with niacin or a fibrate, stating that the benefits should outweigh the increased risk of myopathy. The concern about the combination of niacin with a statin is based on the early case reports that documented myopathy with lovastatin in combination with high doses of niacin (≥2.5 g/d). Because niacin does not alter the pharmacokinetics of lovastatin and because excessive doses of niacin have documented hepatotoxicity, the most likely explanation for the cases of myopathy that are associated with combination statin-niacin therapy is that the liver impairment associated with niacin toxicity results in delayed clearance of the statin, leading to an increased risk of myopathy. Statin-induced myopathy is almost always associated with factors that increase the AUC, such as increased dosage, hypothyroidism, renal or hepatic impairment, or drugs that interfere with statin metabolism, such as cytochrome P450 3A4 inhibitors. In the absence of hepatotoxicity, it is unlikely that niacin would increase the risk of statin myopathy, and since the time of the first two reports of niacin and lovastatin myopathy, there have been no additional reports in the medical literature. Adverse event reports (AERs) under the Med Watch program to the FDA have also documented a very low incidence of statin myopathy associated with niacin.[47] Extended-release niacin, which has a very low rate of hepatoxocity, especially when compared with sustained-release niacin, has very few reports of myopathy in the AER database despite several hundred thousand prescriptions written in combination with a statin. Therefore the AER data, although not conclusive, support the safety of doses of extended-release niacin up to 2 g/d in combination with a statin.

In regard to fibrate therapy, there appears to be a clinically significant difference in safety with the combination of gemfibrozil compared with fenofibrate plus a statin. At least 60 case reports of gemfibrozil-statin myopathy have been in the medical literature compared with 2 cases of fenofibrate in combination with a statin. Reviews of the FDA AER database have documented that after correcting for prescription use, the rate of myopathy for gemfibrozil compared with a statin is 30 times more than combination therapy with fenofibrate (Table 26–7).[48,49] Cerivastatin, in combination with gemfibrozil, was associated with more than 4000 times the rate of rhabdomyolysis compared with statin therapy alone, and numerous fatalities were reported, resulting in the removal of cerivastatin from the worldwide market. An analysis of several managed care prescription and hospitalization event data has estimated that the rate of rhabdomyolysis requiring hospitalization from cerivastatin in combination with gemfibrozil was at least 1 in 10 patients. The Lipid and Diabetes Study (LDS),[50] a 2 × 2 factorial design, used cerivastatin/fenofibrate combination therapy or placebo in diabetics and enrolled more than 2000 patients (more than 1000 for more than 12 weeks) on cerivastatin and fenofibrate before the study was discontinued when cerivastatin was withdrawn from the market. In the more than 2000 patients on the combination of cerivastatin and fenofibrate, there were no case reports of myopathy. In the FIELD trial approximately 1000 patients were on both fenofibrate and a statin, and no cases of rhabdomyolysis were reported. In a Veterans Administration database evaluation during a 2-year period (October 1, 2002 to September 30, 2003), there were 93,677 patients on a combination of gemfibrozil and statin and 1830 patients on

Table 26–7 Reported Cases of Rhabdomyolysis with Fenofibrate + Statin Versus Gemfibrozil + Statin

Medication	No. Cases Reported	No. Prescriptions Dispensed	No. Cases Reported per Million
Fenofibrate + any statin	16	3,519,000	4.55
Fenofibrate + cerivastatin	14	100,000	140.00
Fenofibrate + other statins	2	3,419,000	0.58
Gemfibrozil + any statin	590	6,757,000	87.32
Gemfibrozil + cerivastatin	533	116,000	4,594.83
Gemfibrozil + other statins	57	6,641,000	8.58

fenofibrate with a statin during the evaluation period. During the 2 years of evaluation, there were 149 cases of rhabdomyolysis or acute tubular necrosis in the 93,677 patients on gemfibrozil with any statin for an overall rate of .16%. No cases of rhabdomyolysis or acute tubular necrosis were reported in 1830 patients on fenofibrate with any statin.[51] Therefore the AER data or the information from the LDS study support a much greater safety margin for combining fenofibrate with a statin than gemfibrozil.

The reason for the much greater propensity for gemfibrozil to increase the risk of myopathy with a statin is most likely due to the difference in the pharmacokinetic interactions between the two fibrates. Lipophilic statins are hydrolyzed by the cytochrome P450 enzymes to increase water solubility for renal excretion. Statins are also metabolized by another secondary pathway known as *glucuronidation.* Gemfibrozil uses the same family of glucuronidation enzymes as the statins, but fenofibrate uses a different enzyme family. This explains the marked increase in AUC for statins in conjunction with gemfibrozil, although fenofibrate has no significant effects on statin blood levels. Gemfibrozil is also a potent cytochrome P450 2C8 inhibitor, which is a metabolic pathway for cerivastatin. The more prominent increase in the AUC for gemfibrozil and cerivastatin may be due to both the effect of CYP 2C8 and glucuronidation. Rosiglitazone and repaglinide are also CYP 2C8 metabolized, and blood levels are increased in combination with gemfibrozil but not with fenofibrate. Therefore gemfibrozil is problematic not only for combination therapy with statins but also for use with the antidiabetes drug that uses the CYP 2C8 pathway. In diabetic patients who have documented benefits from statin therapy but a high residual risk, combination therapy with fenofibrate appears the most appropriate add-on treatment to further improve the lipid profile, if necessary, and avoid the significant safety problems associated with gemfibrozil therapy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is underway to determine the enhanced clinical benefit of adding fenofibrate to the regimen of patients with simvastatin therapy, and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial is evaluating the potential clinical benefits of increasing HDL-C with niacin in patients with CHD and the metabolic syndrome.

OMEGA-3 FATTY ACIDS

Since the observation of the marked TG-lowering effects of salmon feeding in patients with severe hypotriglyceridemia, marine omega-3 fatty acids have been used clinically as a therapy for dyslipidemia.[52] In a comprehensive review of human studies, Harris reported that 4 g/d of marine omega-3 fatty acids decreased serum TGs by 25% to 30% with modest increases in LDL of 5% to 10% and a neutral effect on HDL cholesterol (+1% to 3%).[53] A dose-response relationship exists between omega-fatty acid intake and TG-lowering, but even small intakes can produce significant reductions.[54,55] Postprandial triglyceridemia is especially sensitive to chronic fish oil consumption.[56] The mechanisms for other TG-lowering therapies, such as fibrate or niacin, are fairly well established, but for omega-3 fatty acids, the hypotriglyceridemia is not well understood.

Omega-3 fatty acids regulate at least four metabolic nuclear receptors that result in the repartitioning of metabolic fuel (i.e., fatty acids) away from TG storage and toward oxidation (Fig. 26–7). This effect is mediated by a marked reduction in SREBP1-c, the main genetic switch controlling lipogenesis. With reduction in TG synthesis and increase in fatty acid oxidation in the hepatocyte, there is a decreased substrate for VLDL synthesis and secretion. Additionally, omega-3 fatty acid, as an unsaturated fat, may undergo peroxidation that appears to stimulate the degradation of APO B, also resulting in the reduction in VLDL secretion. A reduction in VLDL secretion allows enhanced postprandial chylomicron clearance, but also omega-3 fatty acids appear to directly stimulate lipoprotein lipase activity.[57]

A highly purified, pharmaceutical-grade omega-3 fatty acid, marine fish oil formulation contains high concentrations of eicosahexaenoic acid and docosahexaenoic acid (440 mg EPA and 360 mg DHA, respectively, for a total of 800 mg EPA + DHA), along with 4 mg (6 International Units) vitamin E in each 1 g capsule. Prescription omega-3 fatty marine oils are indicated for treatment of hypertriglyceridemia and have been shown in clinical trials to significantly reduce serum TGs by 19% to 55% at doses of 4 capsules/d when administered over periods from 6 weeks to several years. Marine oil also modestly increases LDL-C, increases HDL-C levels, and favorably affects lipoprotein particle size and subclass distribution. When combined with gemfibrozil and simvastatin, marine oil reduces TG levels an additional 37% and 46%, respectively. Marine oil is well tolerated with few side effects other than mild gastrointestinal-related symptoms. Specifically, no adverse effects have been reported regarding hyperglycemia, abnormal bleeding, elevations in muscle or liver enzymes, or abnormalities in kidney or nerve function.

TORCETRAPIB

Torcetrapib is the first in the class of cholesteryl ester transfer protein (CETP) inhibitors. CETP assists the equal mass gradient transfer of cholesteryl ester from HDL to the ApoB-containing particles (LDL and VLDL) for TGs. In the presence of hypertriglyceridemia, CETP, by transferring TG into HDL and LDL in exchange for cholesteryl ester, results in TG-enrichment of these lipoproteins, which undergo further hydrolysis by lipoprotein and hepatic lipases to form a smaller, more dense LDL and HDL. Therefore the inhibition of CETP results in a marked increase in HDL mass and size by reducing HDL metabolism and also increasing LDL particle size.

The observation of high levels of HDL-C in Japanese populations with deficiencies in CETP[58,59] has led to the concept of CETP inhibition as a potential new strategy for substantially elevating HDL-C and for the treatment of CVD,[60] although it is unclear if families with elevated HDL due to CETP deficiency have a lower rate of CVD. In rabbit models both biologic and chemical techniques have been employed to suppress CETP activity, resulting in increases in HDL-C levels and reductions in atherosclerotic lesions.[61-64] In preliminary trials, torcetrapib, administered alone to healthy young individuals[65] and with or without background statin therapy to individuals with low levels of HDL-C,[66] has been shown to produce substantial elevations in HDL-C, modest decreases in LDL-C, and increases in lipid particle size.

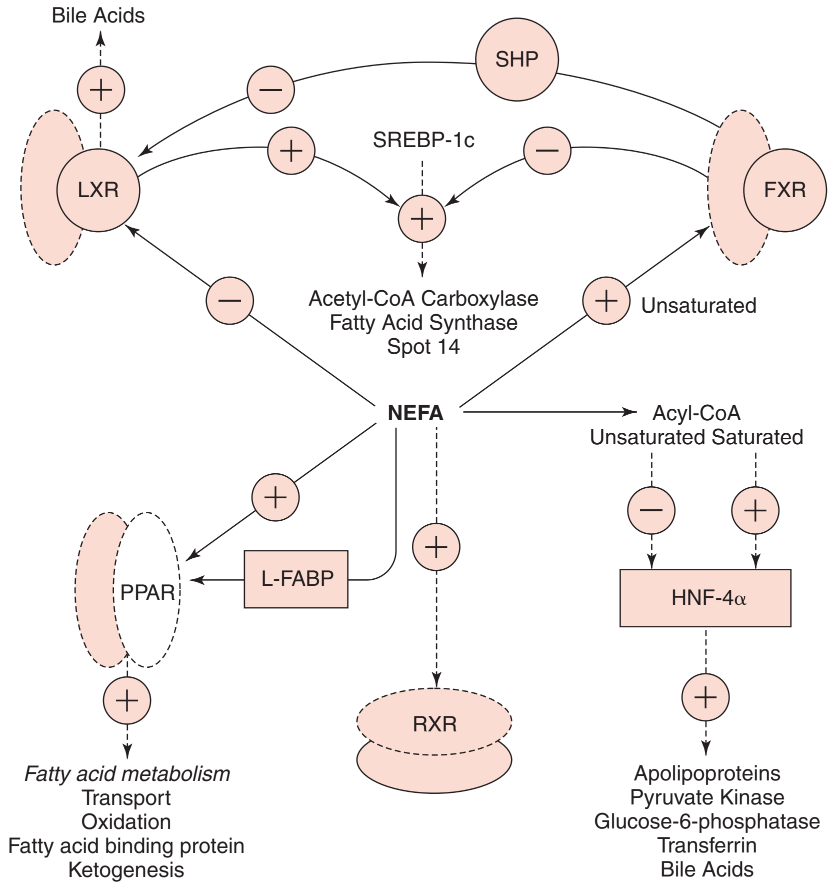


Figure 26–7 Omega-3 fatty acid regulation of metabolic nuclear receptors. NEFA refers to nonesterified fatty acids that are omega-3 polyunsaturated fatty acids but also applies to omega-6 polyunsaturated fatty acids. These fatty acids activate nuclear receptors and cofactors that in turn activate or repress genes that regulate metabolism of lipids, carbohydrates, and bile acids. LXR = liver X receptor; FXR = farnesoid X receptor; PPAR = peroxisomal proliferator activator receptor; HNF-4 = hepatic nuclear factor-4; RXR = retinoid X receptor; FABP = fatty acid binding protein; SHP = small heterodimer partner; SREBP-1c = sterol regulatory element binding protein-1c.

A 60-mg dose of torcetrapib was shown to increase HDL by 45% and lower LDL by 8%.[67] Torcetrapib is generally well tolerated, but there is a dose-related increase in blood pressure. The 60-mg dose, which is the single dose that is being evaluated in a large phase II program, is associated with an approximate 2-mm mean increase in systolic blood pressure. The clinical benefits of torcetrapib on atherosclerosis, as assessed by intravascular coronary ultrasound and by carotid ultrasound and a large cardiovascular morbidity trial, are presently underway to test the hypothesis that raising HDL by CETP inhibition results in a cardiovascular benefit.

CONCLUSION

Reducing the residual CHD risk for patients on statin therapy remains an important clinical challenge. The "lower is better" hypothesis has been well documented by clinical trials, but even with low levels of LDL cholesterol, patients with diabetes, metabolic syndrome, and other uncontrolled risk factors continue to have a relatively high CV event rate. Combination therapy that further improves the lipid profile appears to be frequently necessary for very high-risk patients who have not yet achieved the optional therapeutic target. The use of combination therapy has been tainted by the history of increased risk of myopathy with gemfibrozil in combination with a statin. However, other lipid-altering agents, such as bile acid sequestrants, extended-release niacin, ezetimibe, and fenofibrate, do not have a pharmacokinetic interaction with statins and appear to have a low risk for increasing statin-related side effects. The improved safety of these agents with a statin has stimulated a new era of clinical trials evaluating the potential clinical benefits of combination therapy.

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Drugs for Elevated LDL-Cholesterol

Neil J. Stone

CHAPTER CONTENTS

HMGCoA-REDUCTASE INHIBITORS

HMGCoA-reductase inhibitors, or "statins," are competitive inhibitors of the rate-limiting step of hepatic cholesterol synthesis. This leads to a reduction in hepatocyte cholesterol concentration with subsequent upregulation of low-density lipoprotein (LDL) receptors that enhance clearance of LDL.[1] Statins lower both large and small LDL subclasses.[2] In addition to effects on LDL, intermediate-density lipoprotein (IDL) and very-low-density lipoprotein (VLDL) are decreased by statin therapy.[3] Both fractions are decreased to similar percentages by statin therapy. Thus, statins are effective drugs for lowering both elevated LDL-C and triglyceride-rich lipoproteins. They are indicated in those individuals with elevations of these lipoproteins due to genetic reasons, as in familial hypercholesterolemia, familial defective apo B, familial combined hyperlipidemia, and type 3 (remnant removal disease). They are also indicated in most adults with diabetes,[4] renal failure,[5] and for the dyslipidemia found in renal and cardiac transplantation recipients.[6] The Adult Treatment Panel III (ATP III) recommends statins as the most effective class of drugs for lowering LDL-C in reducing the risk for CHD in both primary and secondary prevention.[7]

Effects on Lipids and Lipoproteins

All members of the statin class reduce LDL-C levels in a dose-dependent fashion. This dose-response relationship is log-linear. This means that although the initial dose lowers LDL-C from 25% to 45%, additional doublings of the statin dose result in only an additional 6% to 7% of LDL-C lowering.[8] Responsiveness to statins by individuals varies, however, and individuals who are hypo- or hyper-responsive to one statin maintain that response with other statins.[9] In familial combined hyperlipidemia, using a moderate dosage of a potent statin generates lowered cholesterol not only in LDL but also in triglyceride-rich remnant lipoprotein (TGRL) in the fasting and fed states.[10] This allows attainment of both LDL and non–HDL-C goals.

The initially available statins (lovastatin, pravastatin, and simvastatin) were derived from fungal fermentation.[11] Subsequently, synthetic forms (fluvastatin, atorvastatin, cerivastatin, and rosuvastatin) became available.[12] Cerivastatin, the most potent of all the statins introduced to date, was withdrawn from the market after it was found to have an unacceptable incidence of myositis and rhabdomyolysis.[13,14] The latter reaction was more likely when cerivastatin was combined with gemfibrozil.

A review of clinical trial data indicated that initial doses of statins (Table 27–1) should provide at least a 30% reduction in LDL-C.[12] Triglycerides are lowered with statins approximately proportional to the degree of LDL-C lowering, 15% to 30%, an effect size that is usually not adequate to normalize moderate elevations of triglycerides.[15] Statin therapy does not result in removal of triglyceride-laden chylomicrons. Thus, statins should not be used when severe hypertriglyceridemia suggesting chylomicronemia is present. Statins affect HDL-C levels to a variable degree, and there is no relationship between degree of LDL-C lowering and change in HDL-C.[16] Rosuvastatin, simvastatin, and pravastatin appear to raise HDL-C more than atorvastatin, for example. In the PROVE-IT-TIMI 22 trial, standard LDL-C lowering with pravastatin in subjects with acute coronary syndrome was associated with a greater percent increase in HDL-C than that seen with the intensive LDL-C lowering with atorvastatin. In PROVE-IT-TIMI 22, those individuals with the greatest LDL-C lowering had the greatest event reduction.[17] Statins in moderate doses do not lower Lp(a), although a study of heterozygous subjects with familial hypercholesterolemia (FH) showed a decrease in Lp(a) levels with 80 mg of atorvastatin.[18] Statins lower markers of inflammation and oxidation, such as high-sensitivity CRP, as well as lipoprotein-associated phospholipase A2 (Lp-PLA2).[19] Statins lower hs-CRP in primary and secondary prevention patients, and the result is seen as early as 12 weeks.[20] For hs-CRP, the lowering is mainly independent of LDL-C lowering, unlike that seen with Lp-PLA2, which is largely mediated by the statin-induced reduction in LDL-C. Lovastatin was effective among those individuals with a ratio of total to HDL-C that was lower than the median and a hs-CRP level higher than the median in a primary prevention trial.[21] In contrast, lovastatin was ineffective among subjects in this trial with a ratio of total to HDL-C and a hs-CRP level that were both lower than the median. Also, patients with acute coronary syndrome who have low hs-CRP levels after statin therapy have better clinical outcomes than those with higher hs-CRP levels, regardless of the resultant level of

LDL-C.[22] Whether hs-CRP should be a co-equal target with LDL-C for CHD risk reduction awaits definitive clinical trial results.

Pharmacokinetic Properties

The available statins differ in terms of lipid solubility, half-life, and hepatic and renal clearance[23,24] (Table 27–2). Several of the statins are metabolized extensively by the CYP pathways of the P450 cytochrome system. Fluvastatin is metabolized by 2C9, whereas atorvastatin, lovastatin, and simvastatin are metabolized by 3A4. Rosuvastatin is only weakly metabolized by 2C9, and pravastatin is not metabolized at all. These properties can have clinical importance. For example, in patients with impaired renal function, atorvastatin and fluvastatin may have advantages because they are essentially not renally cleared. Likewise, for those patients who require prolonged treatment with erythromycin or clarithromycin, antibiotics that inhibit the metabolism of statins by the 3A4 P450 system, such as atorvastatin, simvastatin, and lovastatin, clinicians should consider an alternative statin.

Drug Interactions

Safety is not a class effect because statins vary in their routes of excretion and the impact on their metabolism by other drugs, especially those that affect the P450 system.[25] Statins, especially simvastatin, must be used in low doses and monitored regularly if coadministered with amiodarone or verapamil. Physicians should be aware that erythromycin; clarithromycin; azole antifungals, such as ketoconazole; protease inhibitors; and large quantities of grapefruit juice may increase steady state concentrations of statins. Fluvastatin is metabolized by the 2C9 pathway, and concentrations of fluconazole and warfarin may increase statin concentrations. Because rosuvastatin is only weakly metabolized by 2C9, it does not interact significantly with fluconazole. Pravastatin is not metabolized at all by the P450 system, but protease inhibitors may decrease its concentration. All statins may interact with cyclosporine and with other lipid-lowering drugs, such as fibrates and nicotinic acid; warfarin; and digoxin.[26] Cyclosporine is used extensively in transplant patients. Cyclosporine is highly lipid soluble, and a significant portion is bound to lipoproteins. It increases LDL-C and Lp(a) concentrations. It affects fluvastatin less so.[27] Gemfibrozil affects glucuronidation of statins, resulting in a higher concentration of statin and increased toxicity in turn, which results in an unacceptably high incidence of rhabdomyolysis when combined with cerivastatin. Coadministered fenofibrate does not raise statin concentrations and is now the fibrate of choice when fibrate and statin therapy are combined. Both fluvastatin and warfarin are metabolized by the P450 2C9 pathway. Because case reports have indicated changes in warfarin levels with other statins not metabolized this way, until more definitive data are available, patients on warfarin should monitor their INR closely after starting statin therapy.[28] Statins may increase digoxin concentrations by inhibiting P-glycoprotein transport.[29]

Although there were early reports of myositis with statin and nicotinic acid combinations, this has not been reported in studies of an extended-release form of nicotinic acid.[30] This may relate to the higher incidence of hepatotoxicity with long-acting forms of nicotinic acid and the resultant increased levels of statins that result from hepatic damage.

Efficacy

Angiographic Trials

A decade of double-blind, randomized, controlled angiographic trials demonstrated that treatment with statins could significantly decrease progression of atherosclerosis.[31] Thompson emphasized the importance of statins in lowering non-HDL lipoproteins and LDL-C in these trials. The Post Coronary Artery Bypass Graft Trial (Post CABG) demonstrated the value of lower LDL-C attained with more intensive statin (lovastatin) therapy in those subjects who had undergone coronary bypass surgery.[32] The higher-dose lovastatin group attained an LDL-C of approximately 100 mg/dL as compared

Table 27–1 Statins–Effective Clinical Dosages

Statin Name	Daily Dose to Lower LDL >30%	Maximal Daily Dose
Lovastatin	40 mg	80 mg
Pravastatin	40 mg	80 mg
Simvastatin	20 mg	80 mg
Fluvastatin XL	80 mg	80 mg
Atorvastatin	10 mg	80 mg
Rosuvastatin	5 mg	40 mg

Table 27–2 Statin Pharmacokinetics

Statin	Atorvastatin	Fluvastatin/XL	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Bioavailability	12	19-29/6	5	18	20	5
Lipophilicity	Yes	Yes/Yes	Yes	No	No	Yes
Protein Binding	>98	>99/>99	>95	50	88	95
CYP Metabolism	3A4	2C	3A4	None	2C9-minor	3A4
Active Metabolites	Yes	No/No	Yes	No	Yes (minor)	Yes
Urinary/fecal excretion; %	2/70	6/90, NA	10/83	20/71	10/90	13/58
Hepatic extraction; %	>70	>68,>68	>70	44-66	63	78-87
$T_{1/2}$, hours	15-30	0.5-2.3/4.7	2.9	1.3-2.8	20.8	2-3

Modified from: Ballantyne CM, Corsini A, Davidson MH, et al: Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med 2003;163(5):553-64 and Corsini A, Bellosta A, Davidson MH: Pharmacokinetic interactions between statins and fibrates. Am J Cardiol 2005;96:44K-49K.

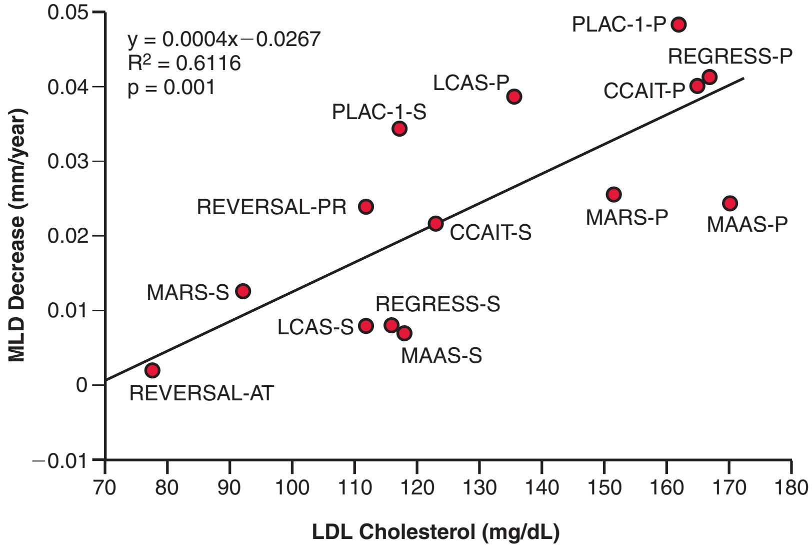

Figure 27–1 Atherosclerosis progression varies directly with low-density lipoprotein (LDL). This regression line indicates that atherosclerosis does not progress when LDL is 67 mg/dL or below. Data from randomized placebo-controlled trials using statins for preventing atherosclerosis progression or preventing coronary heart disease events in primary or secondary prevention were used for computation of the univariate regression lines correlating LDL with outcomes. Regression estimates, model R^2, and *P* values for LDL effect were obtained from the unweighted regression lines. AT, atorvastatin; CCAIT, Canadian Coronary Atherosclerosis Intervention Trial; LCAS, Lipoprotein and Coronary Atherosclerosis Study; MAAS, Multicentre Anti-Atheroma Study; MARS, Monitored Atherosclerosis Regression Study; MLD, mean luminal diameter; P, placebo; PLAC, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study; PR, pravastatin; REGRESS, Regression Growth Evaluation Statin Study; REVERSAL, Reversal of Atherosclerosis with Aggressive Lipid Lowering; S, statin. (From O'Keefe JH, Cordain L, Harris WH, et al: Optimal low-density lipoprotein is 50 to 70 mg/dL; lower is better and physiologically normal. J Am Coll Cardiol 2004;43:2142-46.)

with the reduction of LDL-C to only 132 to 136 mg/dL. The investigators found delayed atherosclerotic progression in the grafts at 4 to 5 years. An informative angiographic trial enrolled 341 subjects with stable coronary disease, relatively normal left ventricular function, and an LDL-C higher than 115 mg/dL who were referred for angioplasty.[33] Those assigned to the high-dose statin therapy (atorvastatin) had a significantly longer time to the first ischemic CHD event as compared with those who were assigned to angioplasty and usual medical care.

Although the CHD event rate was 36% lower in the statin group, the P value obtained was not statistically significant due to the adjustment for multiple on-trial analyses. On closer inspection, the intensive statin therapy had its greatest effect in reducing revascularization procedures and hospitalizations for worsening angina. Using intravascular ultrasound, a multi-center study showed that intensive statin therapy (atorvastatin 80 mg/d) had a significantly greater effect on the primary endpoint (percentage change in atheroma volume) than a moderate dose of a statin (pravastatin 40 mg/d).[34] Importantly, progression did not occur in those assigned to atorvastatin 80 mg/d, whereas it did in those assigned to pravastatin 40 mg/d. Of note, those assigned to atorvastatin 80 mg/d had significantly lower hs-CRP levels than those assigned to pravastatin 40 mg/d. O'Keefe and coworkers plotted out the results of major angiographic trials showing the increasing benefit of LDL-C lowering down to an LDL-C of less than 80 mg/d (Fig. 27–1).[35]

Surface/transesophageal MRI has been used to monitor statin-induced atherosclerotic plaque (AP) reduction.[36] AP regression and reverse remodeling was detected accurately by MRI in just 6 months after statin therapy initiation, and not surprisingly, it was associated with LDL-C reduction.

Large-Scale Clinical Trials

Statins have proven effective in primary prevention and secondary prevention trials (Tables 27–3 and 27–4). As might be expected, the absolute risk reduction is greater in the secondary prevention trials, resulting in a steeper LDL-C-event reduction curve than that seen in primary prevention trials. The large Heart Protection Study demonstrated significant benefit for total mortality and CHD events in subjects at high risk of a coronary event assigned to simvastatin 40 mg daily compared with placebo.[37] This substantial benefit occurred regardless of baseline LDL-C and in all subgroups including women and the elderly. Benefit increased with duration of therapy. Ischemic stroke incidence was also substantially reduced by statin therapy.[38] No significant increase in liver or muscle toxicity occurred, and statin therapy was not associated with an increase in cancer, respiratory disease, or suicide.

The Cholesterol Treatment Trialists' collaboration produced a prospective meta-analysis of data from 90,056 subjects in 14 randomized trials of statins (Fig. 27–2).[39] During a mean of 5 years 8186 subjects died, 14,348 had major vascular events, and 5103 developed cancer. Mean LDL-C differences at 1 year ranged from 14 mg/dL to 69 mg/dL with a mean of 42 mg/dL in these trials. The results mirrored those seen in the Heart Protection Study. A highly significant reduction occurred in all-cause mortality, as well as a significant 19% reduction

Table 27–3 Cardiovascular Benefits of Statins in Secondary Prevention Clinical Trials

Study	Statin Dose; Numbers of Subjects	LDL-C Reduction (%)	Efficacy Against CHD	Efficacy Against Stroke
HEART PROTECTION STUDY (HPS) subjects 40-80 yr old with coronary disease, other occlusive disease, diabetes	Simvastatin 40 mg/d (10,269) vs. placebo (10,267)	–37	Significant reductions in total mortality, fatal and nonfatal MI, revascularization	Yes
PROSPER—subjects 70-82 yr old with history of or risk factors for vascular disease	Pravastatin 40 mg/d (2891) vs. placebo (2913); mean follow-up was 3.2 yr	–32	No reduction in total mortality, but significant reduction in fatal and nonfatal CHD	No, though a decrease in TIA (low rate of stroke in placebo group)
PROVE-IT-TIMI 22—4162 subjects with acute coronary syndrome; mean age 58 yr	Atorvastatin 80 mg (2099) vs. pravastatin 40 mg (2063); mean follow-up was 2.0 yr	Prava 40: –10; Atorva 80: –42	Greater reduction in combined endpoint with atorvastatin 80 mg than with pravastatin 40 mg	No
Cholesterol and Recurrent Events (CARE) Study—4159 subjects post-MI; mean age 59	Pravastatin 40 mg vs. placebo; mean follow-up was 5 yr	–28	Significant reduction of primary endpoint	Yes
Long Term Intervention in Ischaemic Patients (LIPID)—9014 subjects, 31-75 yr old MI and acute coronary syndrome	Pravastatin 40 mg/d (4512) vs. placebo (4502); mean follow-up was 5 yr	–25	Significant reduction of primary endpoint	Yes

in coronary mortality. Nonsignificant reductions occurred in noncoronary vascular mortality and nonvascular mortality. Statin therapy substantially reduced myocardial infarction or CHD death and coronary revascularization by about 25%. The rates for fatal or nonfatal stroke were reduced by 17% on average. The proportional reduction in major vascular events differed significantly ($P < 0.0001$) according to the absolute reduction in LDL-C achieved but remained similar throughout the range of LDL-C studied. These benefits were significant within the first year but were greater in subsequent years. Moreover, statin therapy was found to be safe with no increase in cancer risk. Taken as a whole, this large dataset suggests that in those with known CHD or greatly at its risk, prolonged statin treatment with substantial LDL-C reductions should provide benefit to all patients irrespective of the initial LDL-C. Using ATP III guidelines with LDL-C goals based on CHD risk is still reasonable, however, because the benefits, risk, cost, and feasibility issues must be considered in various patient groups to determine the intensity of therapy.

MECHANISM OF BENEFIT OF STATINS

Although LDL lowering appears to be the major reason why statins produce cardiovascular benefit, some investigators hold that there are “pleiotropic effects” on endothelial dysfunction, inflammation, coagulation, and plaque regression that more fully explain how statins work[40] (Table 27–5). They argue that pleiotropic effects may explain the early benefit seen with statins in the acute coronary syndrome[41] as compared with beneficial but delayed effects in nondrug trials of LDL-C lowering by partial ileal bypass.[42] Whether these effects are truly cholesterol independent and mediated by their ability to block the synthesis of isoprenoid intermediates is actively debated.[43] Others argue that LDL-C reduction may serve as a marker for the pleiotropic effects seen with statins. This is supported by increasing benefit from statins at the higher dosage range.

Safety

As can be seen from the large-scale meta-analysis, in clinical trials, statins are well tolerated. The two major side effects that clinicians encounter are those involving the liver and muscles.

Liver

An ACC/AHA/NHLBI Clinical Advisory on Statins noted that statin-induced elevated hepatic transaminases generally occur infrequently with rates below 2%.[12] These elevations were dose dependent and more likely at the highest dosages. The setting may be important as well. In the PROVE-IT-TIMI 22 Trial, the incidence of significant liver transaminase elevation was 3.3% in the atorvastatin group versus 1.1 in the pravastatin group.[17] In the setting of chronic stable coronary disease, the Treat to New Targets (TNT) trial showed a low order of

Table 27–4 Cardiovascular Benefits of Statins in Primary Prevention Clinical Trials

Primary Prevention Clinical Trials	Statin Dosage	LDL-C Reduction (%)	Efficacy against CHD	Efficacy against Stroke
AFCAPS/TEXCAPS; 5608 men 45-73 yr old and 997 women 55-73 yr old with lipid entry criteria (low HDL-C required)	Lovastatin 20 mg and 40 mg/day (3304) vs. placebo (3301)	-25	Yes	Not mentioned
WOSCOPS; high risk men 45-64 yr old without prior myocardial infarction; follow-up for 4.9 years	Pravastatin 40 mg/d (3302) vs. placebo (3293)	-26	Yes	No
ASCOT-LLA 10,305 hypertensive patients (aged 40-79 yr) with at least 3 other cardiovascular risk factors followed for 3.3 yr before study stopped by DSMB	Atorvastatin 10 mg/d (5168) and placebo (5137)	-29	Yes	Yes
ALLHAT-LLA; 10,355 subjects, aged 55 yr or older who met lipid criteria and were followed for up to 8 yr	Pravastatin 40 mg/d	-16.7 (this small reduction related to drop-ins in placebo + drop-outs in treatment groups)	No; difference in LDL-C between statin and usual care was only 18% due to high cross-over and drop-out rate	No
CARDS; 2838 men and women with type 2 DM and at least one other risk factor[29]	Atorvastatin 10 mg/d	-40	Yes	Yes

liver toxicity and did not differentiate between the low- and high-dose atorvastatin regimens employed. Indeed, it has been questioned whether low-level transaminase elevation (<2× the upper limit of normal) constitutes true hepatotoxicity.

Statin-associated hepatotoxicity has several characteristic features.[44] Elevations of liver transaminases usually are noted within the first 12 weeks of therapy. Unlike the situation with nicotinic acid hepatotoxicity, in which symptoms often herald liver damage, statin-associated elevations of liver transaminases are usually asymptomatic. Evidence of cholestasis with jaundice and hyperbilirubinemia is rare. Progression to liver failure shown to be specifically due to statins is rare; indeed, despite the large number of subjects assigned to statins in large-scale clinical trials, statin-induced liver failure was not seen. When the statin dose is reduced or there is rechallenge with another statin, elevations of liver transaminases often do not occur. When statin therapy is stopped, elevated liver transaminases return to normal. An experience from a large HMO of severe cases of hepatic transaminase elevation (defined as >10× the upper limit of normal) indicated that in 14 of 17 cases in which hepatotoxicity was directly attributable to statin use, there was a drug interaction.[45] Although they concluded that less frequent liver enzyme monitoring was reasonable for most patients on statins, they acknowledged that continued monitoring was warranted for patients who were receiving concomitant medications or who had comorbidity that increased their risk of hepatic toxicity.

Cholestasis and active liver disease are listed as contraindications to statin use. Patients with acute liver disease, such as acute viral hepatitis or alcoholic hepatitis, should not take statins until they have recovered. The review cited earlier noted that statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C, and treatment of hyperlipidemia may actually improve transaminase elevations in individuals with fatty liver.

A reasonable screening approach for those on statins is to check a liver panel 6 or 12 weeks after starting statin therapy and then yearly or after a change in either dosage or the patient's condition. More frequent testing should be considered if there are concerns over the patient's condition, associated drug therapy (e.g., nicotinic acid, fibrates, or other drugs that affect the liver), alcohol habit, or the medical setting (hospital). If the patient has known stable liver disease, such as fatty liver, and merits statin therapy, low doses of statins can be employed initially, but screening should be more frequent. Statin therapy should be stopped if transaminase elevations exceed 2× the upper limit of normal. In the Heart Protection Study there was no significant difference from placebo in liver transaminases >4× the upper limit of normal. However, an important caveat is that subjects in this trial were prescreened for simvastatin tolerability.

Muscle

The ACC/AHA advisory defined several of the terms used to describe muscle problems with statins.[12] These included the following:

Endpoint	Events (%) Treatment (45,054)	Events (%) Control (45,002)	RR(CI)
Nonfatal MI	2001 (4.4%)	2769 (6.2%)	0.74 (0.70–0.79)
CHD death	1548 (3.4%)	1960 (4.4%)	0.81 (0.75–0.87)
Any major coronary event	**3337 (7.4%)**	**4420 (9.8%)**	**0.77 (0.74–0.80)**
CABG	713 (1.6%)	1006 (2.2%)	0.75 (0.69–0.82)
PTCA	510 (1.1%)	658 (1.5%)	0.79 (0.69–0.90)
Unspecified	1397 (3.1%)	1770 (3.9%)	0.76 (0.69–0.84)
Any coronary revascularization	**2620 (5.8%)**	**3434 (7.6%)**	**0.76 (0.73–0.80)**
Hemorrhagic stroke	105 (0.2%)	99 (0.2%)	1.05 (0.78–1.41)
Presumed ischemic stroke	1235 (2.8%)	1518 (3.4%)	0.81 (0.74–0.89)
Any stroke	**1340 (3.0%)**	**1617 (3.7%)**	**0.83 (0.78–0.88)**
Any major vascular event	**6354 (14.1%)**	**7994 (17.8%)**	**0.79 (0.77–0.81)**

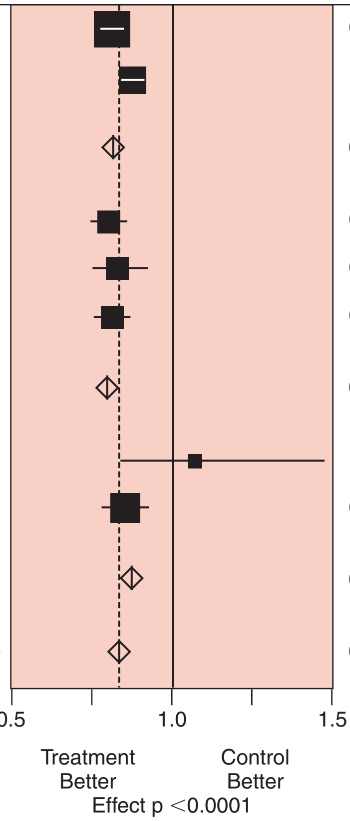

Figure 27–2 Proportional effects on major vascular events per mmol/L LDL cholesterol reduction. The *broken vertical line* indicates overall RR for any type of major vascular event. CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty. The Lesol Intervention Prevention Study (LIPS) only provided data on fatal strokes and so does not contribute to the stroke analyses. *Diamonds* represent totals and subtotals (95% CI). *Squares* represent individual categories (horizontal lines are 99% CIs). The area of square is proportional to the amount of statistical information in that category. RRs are weighted to represent reduction in rate per 1 mmol/L LDL cholesterol reduction achieved by treatment at 1 year after randomization. (From Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267.)

- Myopathy—a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
- Myalgia—muscle ache or weakness without creatine kinase (CK) elevation
- Myositis—muscle symptoms with increased CK levels
- Rhabdomyolysis—muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal and with creatinine elevation (usually with brown urine and urinary myoglobin).

One concerning report detailed four subjects with statin-associated weakness, no CK elevation, and abnormal findings on muscle biopsy.[46] How often this occurs is not clear, but it does indicate that patients with objective measures of statin-associated weakness, irrespective of their CK level, should have their statin stopped until they can be carefully evaluated for other causes of muscle weakness including hypothyroidism and polymyalgia rheumatica. Grundy reviewed the data as to whether statins can cause a low-grade myopathy.[47] He argued that although a small fraction of patients do develop myopathy, the likelihood that there will be progression to rhabdomyolysis and death is small, and this must be balanced against the need for risk reduction with statins in high-risk patients. He emphasized the need for clinicians to look for predisposing conditions of myopathy as listed by the ACC/AHA/NHLBI panel that included advanced age, relatively low body weight, elderly females, certain medications, use of multiple medications, multisystem disease, and acute illnesses or major surgery. The use of combination therapy with gemfibrozil results in additive improvements in the lipid and lipoprotein profile but often with an unacceptable increased risk. Fenofibrate is shown not to affect statin glucuronidation

Table 27–5 Pleiotropic Effects of Statin Drugs[40]

Improve impaired endothelial vasodilation
Produce antithrombotic effects
Decrease vascular inflammation
Decrease vascular smooth muscle proliferation
Increase plaque stability

as is seen with gemfibrozil. This has made fenofibrate the fibrate of choice if it is believed that combination therapy with a statin is beneficial. Additional provocative factors for myopathy are alcohol use, compromised liver or renal function, hypothyroidism, and diabetes (Table 27–6).[48]

Several practical considerations should be noted. First, CK measurements are highly variable. Getting a CK at baseline is useful, but it should be repeated only when symptoms suggest myositis. Second, patients who exercise intensively can have marked asymptomatic excursions in their CK. Moreover, statins magnify the exercise-related increase in CK.[48] The low rate of muscle complications seen in clinical trials may reflect, in some instances, the highly selected nature of the populations studied (e.g., the Heart Protection Study had an "active drug" run-in as compared with the "placebo" run-in phase with the CARE trial).

One useful clinical maneuver for those with vague muscle complaints that are not clearly due to the statin therapy is to provide a 2- to 3-week holiday off statins with a view toward rechallenging with either the same or a lowered dose of the statin to see if the statin is truly causing the symptoms noted. An analysis of the TNT trial showed that discontinuing statins for a short time during the run-in phase did not result in an increased risk of CHD events.[49] For patients with familial muscle disorders or those presenting with new-onset weakness, a work-up should include an inquiry into exogenous substances (alcohol, grapefruit juice, or drugs that increase statin concentrations) and systemic causes (hypothyroidism, collagen vascular disease) and primary myopathy (consider muscle biopsy) should ensue before a consideration of whether to start statin therapy is undertaken.

Fibrates and nicotinic acid can lower LDL-C, but they are mainly used to treat atherogenic dyslipidemia. Fenofibrate can reduce LDL-C by at least 20% in those with normal triglyceride levels.[50,51] In patients with elevated triglyceride levels at baseline, LDL-C lowering is much less and may actually increase. Nicotinic acid lowers LDL-C in a dose-related fashion, but substantial LDL-C lowering of more than 25% usually occurs at doses that exceed 1500 mg per day.[52]

For those patients who require LDL-C lowering above and beyond what statins can provide (e.g., those with familial hypercholesterolemia) or whose intolerance of statin therapy (most often due to muscle symptoms) prevents them from reaching goal levels for LDL-C, drugs that have a primary effect on the gastrointestinal (GI) tract are recommended.

Three classes of drugs are available: bile acid sequestrants (resins, such as cholestyramine and colestipol, and a polymer, such as colesevelam); cholesterol absorption inhibitors, such as ezetimibe; and plant stanol esters.

Table 27–6 Suggestions for Statin Usage

1. Use statins to lower LDL-C with intensity of therapy based on severity of CHD risk. In those at highest CHD risk, statins provide benefit even in those patients with LDL-C lower than 100 mg/dL.
2. If you use statins, lower LDL-C at least 30-40%.
3. Do not consider safety or properties a class effect. Statins differ in pharmacologic properties that can be helpful in deciding which statin to use in an individual patient.
4. Consider muscle and liver toxicity in all patients, even though the overall risk of such a reaction is low. Get a baseline liver panel and if possible, a total CK before starting therapy. Obtain CK and TSH if the patient develops muscle symptoms. Do not measure CK routinely on follow-up blood tests as CK varies widely, especially in those who exercise regularly. Remember that statins can exacerbate exercise-induced skeletal muscle injury.
5. Consider patient characteristics, magnitude of change necessary to reach a goal, associated medications, and comorbidity as factors when you choose a statin. Consider older age, (especially women > 80 yr), small body frame, frailty, multisystem disease, multiple medications, and high-risk clinical situations (perioperative period of major surgery) as factors that might affect the decision regarding statin dosage and the advisability of combined therapy with a fibrate or nicotinic acid.
6. If a nonserious adverse reaction occurs with a patient on a statin, consider rechallenging with a lower dose after the patient is back to baseline, especially if that dose was well tolerated in the past. GI active drugs can be used to obtain the additional LDL-C lowering required if lower-dose statins can be safely taken.
7. Use combinations to optimize effects on lipoproteins. Add GI active medication (bile acid sequestrants, cholesterol absorption inhibitors, stanol ester margarines) to gain additional LDL-C lowering. Add nicotinic acid to raise HDL-C and lower triglycerides, as well as LDL and Lp(a). Add fibrates (fenofibrate is the fibrate of choice for treating high triglycerides/low HDL-C or metabolic syndrome in a patient on statins).

Modified from Stone NJ: Strategies for Treating Abnormal Lipid Profiles with Drugs. In Grundy S (ed): Atlas on Atherosclerosis. Philadelphia, Current Science, 2005, pp 143-166.

BILE ACID SEQUESTRANTS

Bile acid sequestrants (BAS) lower LDL-C by interfering with bile acid absorption in the ileum. They promote the fecal excretion of the bound bile acids resulting in a compensatory increased LDL receptor synthesis to replenish hepatic cholesterol pools, thus producing enhanced LDL clearance. They are nonsystemic drugs for LDL-C lowering either singly or in combination with statins.

Effects on Lipids and Lipoproteins

BAS lower LDL-C in a dose-related fashion (Table 27–7). They are an essential part of a multidrug regimen in patients with FH who have marked elevations of LDL-C because their effects are additive to those seen with statins. BAS allow those who cannot tolerate a higher dose of statin to obtain further LDL-C lowering that is more substantial than that seen with doubling the statin dose. BAS should not be given to those with triglycerides higher than 250 mg/dL due to an increased secretion of triglyceride-rich particles that can produce marked hypertriglyceridemia in some cases. HDL-C levels are increased to a mild degree with BAS. BAS do not lower Lp(a).

For decades, the only BAS available were cholestyramine and colestipol. Before the introduction of statins, these BAS were given in higher dosages than are used currently. They were difficult drugs to use at high dosages due to the limiting gastrointestinal side effects. These resins bound other drugs avidly, especially thyroid replacement hormone, digoxin, and antibiotics. Colesevelam, a polymer gel, was introduced in tablet form.[53] It has the advantage of greater specificity for bile acids and, except for verapamil, has markedly fewer drug interactions than the resins.[54] Combining colesevelam with a low dose of simvastatin 10 mg/d resulted in a mean reduction in LDL-C of 42% that exceeded the reduction usually seen with simvastatin 40 mg/d alone.[55] The effects of combination therapy on serum HDL-C and triglyceride levels were similar to those for simvastatin alone.

Efficacy

In primary prevention, cholestyramine was used in the Lipid Research Clinics Primary Prevention Trial (Table 27–8). It reduced rates of fatal and nonfatal MI, but the trial was not powered to reduce the total mortality rate.[56] In two small angiographic trials, the NHLBI Type II Intervention Study[57] and the STARS[58] trial, hypercholesterolemic men with CHD on cholestyramine had reduced progression on serial angiograms. In the FATS trial, colestipol was added to either nicotinic acid or lovastatin and contributed to the decreased progression on angiography, as well as to the event reduction seen in that trial when compared with a placebo group.[59]

Table 27–7 Bile Acid Sequestrants (BAS)

BAS	Initial Dosage	Maintenance Dosage	LDL-C Lowering Seen (Dosage)	Comments
Cholestyramine resin	8 g/d in divided doses	16-24 g/d as monotherapy; lower doses if used with statins	Varies from 8.7% to 28% depending on dosage of resin	Take other drugs 1 hr before or 3 hrs after; psyllium augments action
Colestipol resin	10 g/d in divided doses	16-24 g/d as monotherapy; lower doses if used with statins	Similar to cholestyramine, varies with dosage of resin	Take other drugs 1 hr before or 3 hrs after; psyllium augments action
Colesevelam	625 mg × 2 or 3 tablets twice daily (7 daily is maximal)	625 mg × 3 bid; can be used as 7 tablets daily if required	LDL-C lowering 19% (3.8 g/d)	Take with a large glass of water

Table 27–8 Clinical Efficacy of Bile Acid Sequestrants (BAS)

Clinical Trials with BAS	Subjects	Drugs (Dosage)	LDL-C Reduction Seen (%)	Efficacy Against CHD
LRC PPT	3806 men	Cholestyramine (16-24 g/d)	-20.3	Yes; 19% reduction in fatal, nonfatal MI at 7.4 yr
STARS	26 men	Cholestyramine 16 g/d	-35.7	Yes; improvement on angiography at 2 yr
NHLBI Type 2 Trial	116 men and women	Cholestyramine 16 g/d average	-26	Yes, if narrowing >50% at baseline at 5 yr
CLAS	162 men	Colestipol 30 gm/d + nicotinic acid 4.3 g/d	-43	Yes; those patients treated had significantly more regression noted on angiography at 2 yr
FH-SCOR	72 men and women	Colestipol, nicotinic acid, and lovastatin	-39	Yes, angiographic change correlated with change in LDL-C at 2 yr
FATS		Colestipol 30 g/d; and either lovastatin 20 mg bid or nicotinic acid 4 g/d	-46 (lovastatin) -36 (nicotinic acid)	Nicotinic acid group had higher HDL than lovastatin group; significant angiographic, clinical improvement at 2.5 yr

Safety/Compliance Issues

BAS are not absorbed and should not be considered systemic drugs. Indeed, GI side effects such as constipation and aggravation of hemorrhoidal bleeding can be limiting. Resins, such as cholestyramine and colestipol, are available as powders that must be mixed with water or applesauce. Colestipol is also available in tablet form. Colesevelam is available in tablet form and should be taken twice daily with a large glass of water. These drugs require detailed patient instruction to be sure that patients take measures to minimize constipation and, in the case of resins especially, guard against drug interactions.

Ezetimibe (Cholesterol Absorption Inhibitors)

Ezetimibe, a 2-azetidione, is a potent inhibitor of cholesterol absorption. Using a genetic approach, investigators identified Niemann-Pick C1-Like 1 (NPC1L1) as a critical mediator of cholesterol absorption and the direct target of this drug.[60] After absorption, ezetimibe is rapidly glucuronidated by the liver and recycled by the enterohepatic circulation to its target site in the brush border of the small intestine. It prevents the absorption of cholesterol from both dietary and especially biliary sources. It markedly reduces absorption of plant sterols.

Defects of either of two cotransporters (ABCG5 and ABCG 8) responsible for resecreting absorbed plant sterols back into the intestinal lumen lead to the rare inherited disease of phytosterolemia. Phytosterolemia is characterized by hyperabsorption and diminished biliary excretion of plant sterols. Because ezetimibe interferes with NPC1L1, reducing the intestinal uptake of cholesterol and plant sterols, it is a novel treatment for this rare disorder.[61]

Effect on Lipids/Lipoproteins

Ezetimibe is used at a single dosage of 10 mg/d. It lowers LDL-C approximately 20%, and its LDL-C lowering effects are additive to those obtained with statins. Although it has been proposed as monotherapy in subjects who are intolerant to statins, no outcome data have confirmed that the combination of a lower dose of statin plus ezetimibe is as efficacious as a larger dose of statin. For statin-intolerant patients or in those with FH, a combination of ezetimibe and a BAS, such as colestipol, results in an additional 20% reduction in LDL-C than seen with either one alone.[62] Patients should avoid taking BAS and ezetimibe at the same time for optimal efficacy.

Efficacy

As note earlier, no randomized clinical trials of ezetimibe with CHD endpoints are available. Although patients with the homozygous form of FH are often resistant to statins, they respond to ezetimibe.[63] Thus ezetimibe becomes a valuable fourth drug alongside statins, BAS, and nicotinic acid.

Safety

For most patients, ezetimibe is remarkably well tolerated with a profile similar to that seen with placebo. In patients who previously had experienced myalgia with statin therapy (with or without elevated CK levels), myalgia has occurred with ezetimibe. Patients with a history of statin intolerance should be monitored for adverse muscle events during treatment with ezetimibe.[64] Elevations of liver transaminases and cases of hepatitis have been reported in patients treated with ezetimibe. Patients who begin ezetimibe should have a liver panel at baseline. After 6 to 12 weeks, measurement of hepatic transaminases is recommended. This should be repeated if combined with a statin. Statins or ezetimibe, or both, are contraindicated for patients with active liver disease or unexplained persistent elevations of liver transaminases.

PLANT STANOL ESTERS

Plant sterols are ubiquitous in nature and have the familiar multi-ring nuclear structure of the sterol family. They differ from cholesterol (found in animals as a key component of cell membranes, vitamin D, adrenal and gonadal steroids) only in the structure of their side chain. Saturated sterols, termed *stanols,* lack the 5 double bond in their B-ring.[65] Saturation of sitosterol, the most commonly occurring plant sterol, gives rise to sitostanol; saturation of campesterol gives rise to campestanol. Plant sterols and cholesterol are consumed approximately in equal amounts, but phytosterols occur in human plasma in a concentration that is normally <0.5% that of cholesterol. Plant stanols are even less well absorbed from the intestine and have a plasma level that is only one tenth as high (i.e., 0.05% that of cholesterol). The ATP III report suggested that the addition of plant stanol or sterol esters and fiber could help patients reach LDL-C goals without having to resort to medications. Because there had been no rigorous comparison of plant stanol and sterols, ATP III recommended either one.[66] Data that became available subsequent to the ATP III report indicate that there may be an advantage to using plant stanol esters rather than plant sterols to lower LDL-C.[67] LDL-lowering efficacy of plant sterol esters tends to diminish over time, whereas in contrast, plant stanol esters maintain their LDL-C lowering efficacy of about 10% from baseline. Also, plant stanols were found not to affect bile acid synthesis, unlike plant sterols. Finally, dietary plant stanol esters reduce statin-induced elevations of serum plant sterol levels, whereas serum plant sterol levels are not lowered when dietary plant sterol ester is fed.[68]

Effect on Lipids/Lipoproteins

An important practical observation is that the margarine-based stanol ester is as effective in a single dose as it is when taken in three divided doses.[69] The persistence of the single-dose effect suggests that stanols not only compete with cholesterol for micellar solubilization but also have an additional, longer-lasting effect on intestinal mucosal cells. There are practical limits to how much margarine an individual can ingest. Maximal LDL-C lowering with plant stanols occurs with 2 g/d of plant stanol esters.[70] In a study of post-menopausal women, LDL-C levels were lowered 13%, which might allow low-risk patients to avoid drug therapy. Older patients appear to be more responsive than younger ones to the effects of plant stanol esters.[71]

Efficacy Against CHD

No CHD endpoint studies are available. Some researchers have raised concerns that elevated plant sterol concentrations could increase CHD risk. To determine whether plasma levels of plant sterols were associated with coronary atherosclerosis in humans, 2542 subjects, aged 30 to 67 years, who underwent electron beam computed tomography had plasma levels of cholesterol and plant sterols measured.[72] Plasma levels of cholesterol, but not sitosterol or campesterol, were significantly higher in subjects with coronary calcium. In addition, in the same paper, investigators could not show that elevated plasma levels of plant sterols (sitosterol and campesterol) were associated with atherosclerosis in genetically modified mice.

Safety

A meta-analysis presented at a workshop on plant stanol esters indicated that levels of vitamins A and D are not affected by stanols or sterols.[73] Alpha carotene, lycopene, and vitamin E levels are carried on LDL particles and remained stable relative to LDL levels. Although beta carotene levels declined, the panel did not expect adverse health outcomes. Indeed, there are adverse health outcomes from beta carotene supplementation.[74] Some experts have suggested that sources of carotenoids be ingested at meals other than when plant sterol esters are eaten.

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Cardiovascular Disease and Lifestyle Modification

Frank M. Sacks and Kathy McManus

CHAPTER CONTENTS

Because of the difficulty many of our patients have in improving their diet, physicians are tempted to lose faith in a nonpharmacologic approach. In this chapter we describe the strong scientific base that supports our continued enthusiasm in clinical practice for healthy nutrition and regular exercise and provide practical approaches to illustrate how to achieve lifestyle modification on a daily basis for our patients.

Epidemiology worldwide shows a pattern of cardiovascular disease (CVD) prevalence that points directly at poor nutritional quality, too much food, and erosion of a healthy lifestyle as the causes of high rates of CVD worldwide. Very low rates of CVD still exist in Mediterranean countries, Japan, and China, where traditional diets and lifestyles are often maintained. During the transition to a developed economy typical of North America and Europe, CVD and diabetes increase rapidly, as has been evident worldwide, notably in South Asia and Latin America.

Although drug therapy for hyperlipidemia has enjoyed huge success in decreasing CVD, national guidelines rightfully still call for nutrition and exercise for primary prevention.[1] For secondary prevention, nutrition and drug therapy should be used together. Diet and drug treatments are additive in improving risk factors, such as LDL cholesterol, blood pressure, and insulin resistance, and reducing CVD. Improved quality of the diet reduces CVD whether body weight remains in excess.[2,3] However, weight loss has its own benefits to raise HDL cholesterol, lower triglycerides, improve insulin sensitivity, and lower blood pressure. When adopted intensively, diet and weight loss, taken to their full potential, may eliminate the need for drug therapy for hyperlipidemia, hypertension, or type 2 diabetes, or simplify the evermore complex multidrug regimens necessary to control these conditions.

DIETARY FATS AND BLOOD LIPIDS

Saturated fats, trans-unsaturated fats from partially hydrogenated vegetable oils, and cholesterol itself increase blood LDL cholesterol.[4,5] Saturated fat and cholesterol are present mainly in dairy fat and red meat, whereas trans fats are present in most fried foods and baked products in the United States. Trans fatty acids are also present in dairy and meat fat, formed in the ruminant gut by bacteria during digestion. All guidelines call for reduction in these dietary lipids. When saturated fat, trans fats, and cholesterol are all reduced, LDL cholesterol decreases. This happens with whatever nutrient replaces it, and this is the rationale for traditional guidelines to recommend a low-fat, carbohydrate-rich diet as a pragmatic way to reduce unhealthy fats.[1] The remaining question is whether nutrients and foods other than those that are carbohydrate-rich could replace the unhealthy fats. The possibilities are unsaturated fats and oils and protein. Beneficial potentials of unsaturated fats are long established, and new mechanisms are still being discovered.[6,7] Moreover, the benefits of protein to improve CVD risk are now just coming to light.[8,9]

The effects on blood lipids and blood pressure of these approaches that emphasize either carbohydrate, unsaturated fats, or protein were compared in the OmniHeart trial, which is discussed later.[8]

High-Carbohydrate, Low-Fat Diets to Reduce LDL Cholesterol and Blood Pressure

Low-fat, high-carbohydrate diets reduce LDL cholesterol generally by a modest amount, 5% to 10%, in proportion to adherence.[5] Very low-fat, low-cholesterol diets can reduce LDL cholesterol more, but acceptability by the general public may be limited. Very low-fat diets may be deficient in essential fatty acids.

Low-fat, high-carbohydrate diets not only reduce LDL cholesterol but also reduce HDL cholesterol and raise triglycerides (Fig. 28–1).[5,6] Because the LDL/HDL ratio is unchanged, CVD risk cannot be assumed to decrease.

The DASH Diet: A Type of Low-Fat, High-Carbohydrate Diet to Control Blood Pressure and LDL Cholesterol

The Dietary Approaches to Stop Hypertension (DASH) study attempted to combine information from epidemiology and animal studies on possible new dietary means to prevent and treat hypertension.[10] Whereas weight loss and dietary sodium reduction had long been shown to lower blood pressure,

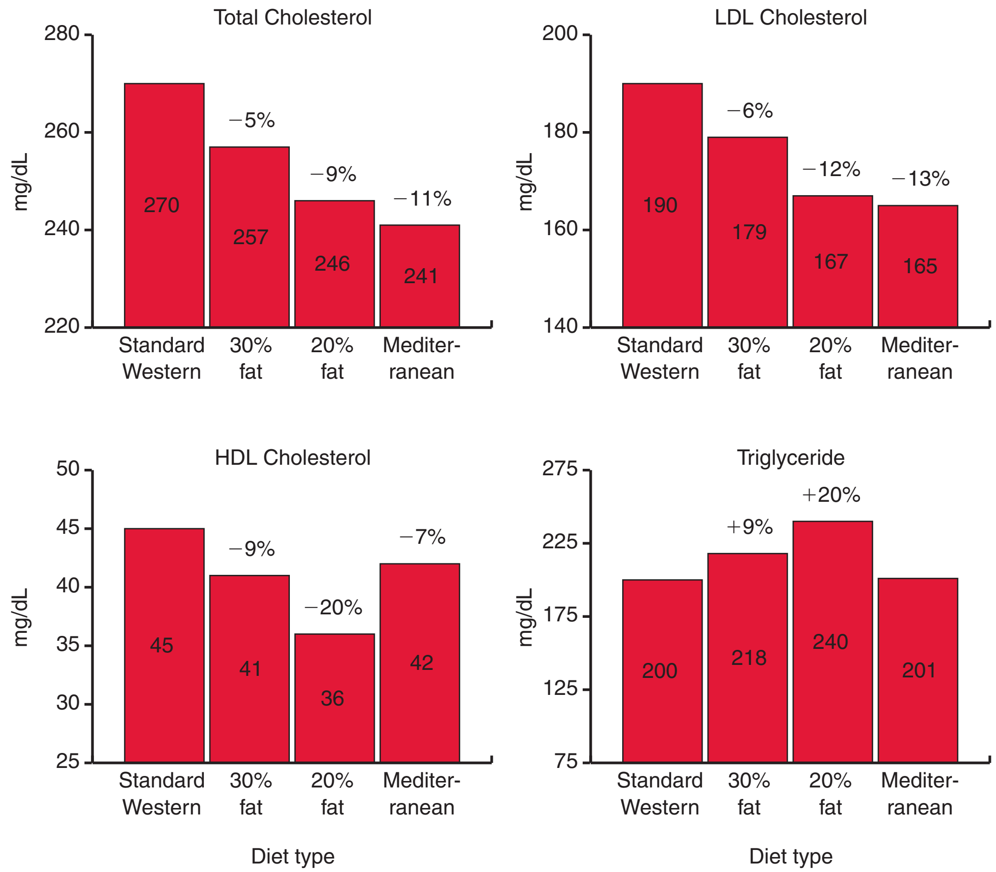

Figure 28–1 Effect of cholesterol-lowering diets on blood lipid risk factors. (Modified from Sacks FM, Katan M: Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. Am J Med 2002;113[Suppl 9B]:13S-24S.)

population studies suggested that other nutrients also may have beneficial effects. The DASH research group designed a dietary pattern that was rich in fruits and vegetables and low-fat dairy products, included nuts and whole grains, and was low in red meat and sugar-containing desserts and beverages. The DASH diet substantially reduced blood pressure and extended the potential for nutritional control of hypertension.[10] When the DASH diet was combined with reduced sodium, the beneficial effects were even stronger (Fig. 28–2).[11] In the typical older patient population in clinical practice, the DASH diet with low-sodium content reduced systolic blood pressure by 15 mm Hg in those with mild hypertension and 10 mm Hg in those with above-average blood pressure (120 to 139 mm Hg),[12] now termed "prehypertension" by Joint National Committee 7.[13]

The DASH diet also reduced LDL cholesterol, as would be predicted from its low content of saturated fat and cholesterol.[14] However, HDL cholesterol also decreased predictably by about the same percentage as LDL cholesterol, and the ratio did not change. Interestingly, triglycerides did not increase on the DASH diet, as they often do on a high-carbohydrate diet. Perhaps this is because of the relatively good type of carbohydrates used in the diet, causing reduced blood glucose response (i.e., having low glycemic index).[15] Overall, predicted CVD risk was reduced on the DASH diet due to its benefits of lower blood pressure and LDL cholesterol outweighing the reduced HDL cholesterol.[14] With low sodium, CVD risk on the DASH diet improved more. DASH is considered the benchmark dietary pattern recommended by the U.S. Dietary Goals Committee.[16]

Low-Fat Diets and Cardiovascular Disease: Clinical Trials and Epidemiology

Low-fat diets have not yet had a satisfactory test in a randomized clinical trial with clinical endpoints. The Women's Health Initiative (WHI) was such a trial in 160,000 women in the United States. These women were randomized to either a low-fat, high-carbohydrate diet rich in fruits and vegetables or to a no-intervention comparison group and followed for 7.5 years. No effect on CVD endpoints and cancer occurred.[17] Although the WHI set a goal for reducing total fat to 20%, it was clear from lack of HDL reduction or triglyceride increase, both biomarkers of dietary fat reduction, that the participants were able to reduce fat only minimally. Previous small-scale trials did not find reduction in CVD with low-fat diets.[5] Ornish and colleagues[18] used a very low-fat, vegetarian diet as a major part of overall lifestyle change that included intensive exercise in a small group of patients with CHD. Meals were provided to the patients. Coronary stenosis improved in the treated group, although the study was not large enough to evaluate an effect on clinical events. A less intensive program of a low-fat diet and exercise in Heidelberg, Germany, also found benefits on coronary stenosis.[19] Epidemiologic data generally have not

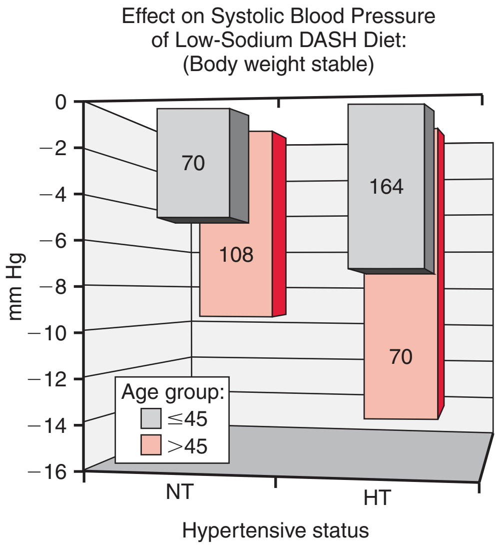

Figure 28–2 Effect of the low-sodium DASH diet on systolic blood pressure. (Modified from Vollmer WM, Sacks FM, Ard J, et al: Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-sodium trial. Ann Intern Med 2001;135:1019-28.)

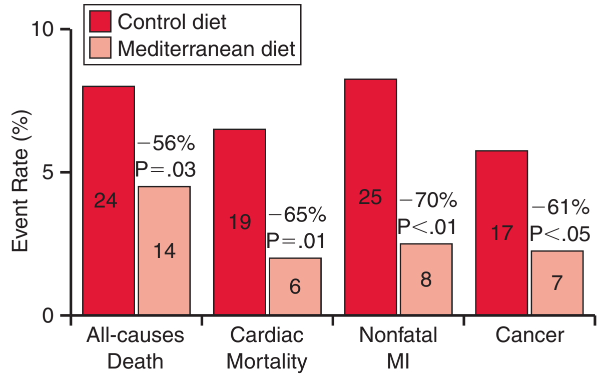

Figure 28–3 The Lyon Heart Study. A trial of a Mediterranean diet in patients after myocardial infarction. (Modified from de Lorgeril M, Renaud S, Mamelle N, et al: Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454-9.)

found a relationship between amount of total fat and CHD.[20] A low-fat dietary pattern can be based on healthy foods, such as whole grains, fruits and vegetables, low-fat dairy products, fish and lean meats, or it can have plenty of high-carbohydrate, high-calorie foods, such as refined flour products, desserts, and sugar-containing drinks. The type of low-fat diet may be critical to its success or failure for risk factor improvement.

Effects of low-fat, high-carbohydrate diets on the CVD risk factors and CHD are as follows:

- Reduction in blood pressure
- Reduction of LDL cholesterol concentration
- Reduction of HDL cholesterol concentration
- No effect on the LDL-to-HDL cholesterol ratio
- Increase in triglycerides, unless low glycemic index foods predominate
- Improvement in coronary stenosis (with an intensive exercise program)
- No reduction in CHD in epidemiologic studies or small-scale, short-duration trials
- No reduction in CVD in the definitive WHI

Moderate Unsaturated Fat Diets

Replacing saturated fat with unsaturated fat has a long history in cardiovascular disease prevention. In the 1950s and 1960s, polyunsaturated vegetable oils from corn, soybeans, and safflower seeds were used essentially as medicine, lacking effective and well-tolerated drugs, to lower blood cholesterol. These polyunsaturated oils are the most potent LDL-lowering nutrients, and several clinical trials demonstrated significant reduction in CVD.[5] A different type of unsaturated oil is canola (rapeseed) oil, which is mainly monounsaturated fat but also has an omega-3 fatty acid, α-linolenic acid. The Lyon Heart Study used this type of oil with a Mediterranean diet in a secondary prevention study that found reduction in CVD (Fig. 28–3).[21] α-Linolenic acid, also prevalent in soybean oil and some vegetable products, is strongly protective against CHD in epidemiologic studies.[22] Finally, olive oil and high-monounsaturated varieties of sunflower and safflower oils have primarily monounsaturated oils. This class of vegetable oil improves risk factors, although a clinical endpoint trial has not been done.

Whatever unsaturated fat is used to replace saturated and trans fat, whether unhydrogenated liquid vegetable oils (e.g., canola, olive, sunflower, safflower, peanut, soybean) or from nuts, total fat intake can be made to remain the same or it can be increased to replace some carbohydrate. Currently, there is uncertainty whether polyunsaturated or monounsaturated fat is superior for preventing CHD, although current evidence tends to favor polyunsaturated oils. Polyunsaturated fats have slightly more effect than monounsaturated fat in lowering LDL levels[4,5] and perhaps in reducing serum inflammatory markers.[6] Any type of fat raises HDL cholesterol and lowers triglycerides compared with carbohydrate. However, as discussed later, the type of carbohydrate food may relate to its metabolic effects.[15] High unsaturated fat diets improve the lipid profile not only compared with saturated fat but also with carbohydrate.

Randomized trials definitively show the benefits of polyunsaturated fats. Three[23-25] out of four[23-26] randomized trials showed significant benefits on coronary rates (Table 28–1). In addition to lowering LDL, polyunsaturated fats may reduce the vascular inflammatory response and limit the propensity of LDL particles to bind to vascular cells and deposit their cholesterol in vascular intima.[6,7] In monkeys, polyunsaturated fats from vegetable oils actually regressed coronary atherosclerosis.[27] Polyunsaturated fats also have anti-arrhythmogenic actions.[28] Thus, much evidence exists for the use of polyunsaturated oils to replace saturated fats to prevent coronary disease.

Monounsaturated fat has less of a direct relationship to coronary prevention compared with polyunsaturated fat. Epidemiology shows modest reduction of CHD at the borderline of statistical significance.[20] A clinical trial that specifically raised monounsaturated fats to prevent CHD has not occurred. Monkey models of atherosclerosis do not show a benefit of monounsaturated fats.[27] However, in humans,

Table 28–1 Clinical Trials of Diet Therapy with Polyunsaturated Vegetable Oils to Reduce Coronary Events: Substitution of Polyunsaturated Fat for Saturated Fat

	N	Dietary Fat	Duration	▲Cholesterol	▲CVD
Finnish Mental Hospital	676	34%	6 yr	–15%*	–43%*
Oslo	412	39%	5 yr	–14%*	–25%*
MRC Soy Oil	393	46%	4 yr	–15%*	–12%
Los Angeles	846	40%	8 yr	–13%*	–34%*

*$P \leq 0.05$.
▲Cholesterol, percentage change in serum cholesterol in the treatment group compared with the change in the control group; ▲CVD, percentage difference in coronary event rates in the treatment compared with the control group.
CVD is defined as myocardial infarction or sudden death for the Finnish, Oslo, and MRC trials and myocardial infarction, sudden death, or stroke for the Los Angeles trial.
Trials with at least 2 years of average follow-up were included.

Table 28–2 Beneficial Effects on Blood Pressure and Blood Lipids of Replacing Carbohydrate with Either Protein or Unsaturated Fat (Omni Heart Study)

	Mean Change from Baseline in Each Diet			
	Baseline	CARB	PROT	UNSAT
LDL (≥130)	157	–20	–24	–22
HDL	50	–1	–3	0
TG	102	0	–16	–9
SBP	146	–13	–16	–16
Risk Reduction		16%	21%	20%

CARB, carbohydrate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PROT, protein; SBP, systolic blood pressure; TG, triglyceride; UNSAT, unsaturated fat.

monounsaturated fats decrease LDL and preserve HDL and TG levels nearly as much as polyunsaturated fats. Monounsaturated oils, particularly olive oil, have been an integral part of the centuries-old traditional Mediterranean diet, which has been associated with very low coronary rates.[29] Thus, there are reasons to advocate increased intake of unsaturated oils from a variety of sources, monounsaturated and polyunsaturated.

Reduced-Carbohydrate, Higher Unsaturated Fat, and Protein Diets: A New Twist to the DASH Dietary Approach

The DASH diet, considered the benchmark diet for health in the United States,[16] is low in fat and high in carbohydrate. Although it reduced blood pressure and LDL cholesterol, it reduced HDL cholesterol and did not affect triglycerides.[14] In view of the favorable evidence on unsaturated fats and HDL and triglycerides, it was hypothesized that the DASH diet could be improved in its overall effects on CVD risk factors by replacing some of the carbohydrate with unsaturated fats. In addition, higher protein intake, replacing carbohydrate, was predictive of reduced blood pressure and CVD in epidemiologic studies, and small-scale studies found favorable effects on lipid risk factors. The OmniHeart study (Optimal Macronutrient Intake) designed three healthful diets, one high in carbohydrate like the DASH diet, another high in unsaturated fat, and a third high in protein, from mixed sources.[8] All three were low in saturated fat and cholesterol and high in potassium, fruits, vegetables, nuts, and low-fat dairy products, thereby building on the dietary approach of DASH. All three diets substantially improved blood pressure and LDL cholesterol. However, lowering carbohydrate intake by either raising unsaturated fat or protein further reduced blood pressure and reduced triglycerides. The unsaturated fat diet raised HDL cholesterol, whereas the protein diet lowered LDL cholesterol and HDL cholesterol (Table 28–2).[8] Taken together, moderate reduction in carbohydrate intake, from 58% to 48% of total calories, produced 11% to 13% further reduction in estimated CVD risk beyond the 20% effect of the DASH-type diet.

Type of Carbohydrate

The usual mix of carbohydrates in the Western diet contains much refined polysaccharides, such as in bread and baked goods, and sugars in juices and soda. These have a high glycemic index, causing glucose and insulin to rise substantially.[15] Other types of carbohydrates that are in whole grains and vegetables have a lower glycemic index because the digestion and absorption of the glucose are slow. These cause less of a rise in blood glucose and hence insulin. The low glycemic index of grains and vegetables is partly explained by the fiber content of these foods but also by the intrinsic digestibility of the food. These foods also cause less of a rise in plasma triglycerides than the more commonly eaten higher glycemic index carbohydrates. Some of the concerns about a low-fat diet can be set aside if a patient truly eats low-glycemic index foods rather than the ubiquitous less-desirable, high-carbohydrate

foods that all too often are a major part of low-fat diets. This concept needs to be put to a definitive test, however.

Effects of reduced-carbohydrate, high unsaturated fat diets on CVD are as follows:

- Reduction in blood pressure
- Reduction in LDL cholesterol concentration
- Preservation of HDL cholesterol concentration
- Reduction in the LDL-to-HDL cholesterol ratio
- Decrease in triglycerides compared with low-fat diets
- Reduction in CVD events (polyunsaturated fats)

The effects of increased protein and lower carbohydrate intakes are as follows:

- Lowered blood pressure
- Lowered LDL cholesterol
- Lowered HDL cholesterol
- Lowered triglycerides
- Lowered CVD risk in epidemiologic studies
- CVD not directly studied in a randomized trial

Fish Oil to Prevent CHD

In the early 1980s, two lines of evidence coalesced to engender widespread excitement on the potentially cardioprotective effects of omega-3 fatty acids, particularly those from fish oil (EPA, DHA). Populations eating large amounts of fatty fish had low rates of CVD, and in many epidemiologic studies, n-3 PUFA intake or blood levels are inversely related to CVD.[30,31] Omega-3 fatty acids are metabolized to prostaglandins and leukotrienes that are anti-thrombotic, anti-inflammatory, and vasodilating. The most established benefit of fish oil is to reduce blood triglycerides. A large dose is necessary, requiring 10 to 15 1-g capsules of fish oil that contain between 20% and 50% omega-3 fatty acids. A prescription version of fish oil that is 90% omega-3 fatty acids is available. This requires fewer capsules. Use of fish oil for hypertriglyceridemia is discussed in Chapter 26.

Polyunsaturated fatty acids either from fish or plants have other anti-inflammatory properties that are still being discovered.[7] Epidemiologic studies show that omega-3 fatty acids are associated with reduced CVD events, both fatal and nonfatal.[30,31] Fish oil and other polyunsaturated fatty acids have potentially anti-arrhythmic effects, increasing the depolarization threshold of ion channels.[28] Reduction in fatal CHD events has been reported in epidemiologic studies often attributed to reduced sudden death. However, a broader view of the benefits of omega-3 fatty acids is necessary because sudden death cannot account for all CVD event reduction, nonfatal as well as fatal, found in epidemiologic studies and clinical trials.

The Diet and Reinfarction Trial (DART) tested the effect of increased intake of fatty fish or fish oil (1.5 g/day) for 2 years in 2033 Welsh men who had had an acute myocardial infarction.[32] This small amount of fatty fish or fish oil significantly reduced total and coronary mortality. Nonfatal myocardial infarction was not affected significantly, however. These results have been reinforced by the GISSI Prevenzione trial, which tested 1 g/day of n-3 polyunsaturated fatty acids in 11,324 Italian patients surviving a recent myocardial infarction.[33] In both trials the death rate began to lessen in the fish oil group as early as 3 months after treatment was started. Recent trials to specifically test the effect of fish oil on cardiac arrhythmia produced mixed results.[34,35] In November 2005, results were reported from a Japanese trial of primary prevention of CVD with fish oil showed striking reduction in nonfatal CVD events.[36] Thus, relatively low doses of fish oil, 1 to 2 g/day, may be cardioprotective due to several mechanisms yet to be determined specifically.

Effects of fish oil intake are as follows:

- Large doses (>5 g/day omega-3 fatty acids)
  - Reduction in blood triglycerides
  - Reduction in blood pressure
  - Anti-thrombotic
- Small doses (1 to 2 g/day omega-3 fatty acids)
  - Prevent CVD events, fatal or nonfatal

OBESITY

In this section we briefly discuss the increasing problem of obesity and then provide a practical approach for evaluating obesity and its treatment. We cover energy intake requirements for weight loss and weight stability, the influence of carbohydrate, fat and protein on success in weight loss, and specific dietary approaches.

The prevalence of obesity and overweight continues to increase despite public health education on healthy eating and exercise. The achievement and maintenance of a healthy weight can contribute to the reduction of risk factors for cardiovascular disease including dyslipidemia, diabetes, and high blood pressure. However, the role of excess dietary fat, protein, and carbohydrate in causing excess weight and in its treatment continues to be debated. To date, most of the published research has involved short-term trials (<1 year duration). Current available data on long-term weight loss are limited. Typically reported weight losses remaining after 4 to 5 years are about 3% to 6% of initial body weight.[37] A 5% weight loss does have health benefits including reduction in lipids and serum glucose levels. Research that supports healthy eating patterns and lifestyle modification to attain and sustain weight over an extended period of time is necessary. Strategies aimed at reducing obesity, and the morbidity and mortality from the chronic diseases associated with it, may be more effective if success also includes quality of life.

Two thirds of adults in the United States are overweight, and 32% are obese according to the 2003-2004 National Health and Nutrition Examination Survey (NHANES).[38] Overweight is defined as an excess of body weight compared with height. Obesity is defined by the National Institutes of Health consensus panel as an abnormally high proportion of body fat.

Body Mass Index as a Measure of Overweight

A variety of methods are used to determine if someone is overweight or obese. Some are based on the relationship between height and weight; others are based on measurements of body fat. The most commonly used method is body mass index (BMI). BMI can be used to screen for both overweight and obesity in adults. It is a calculation based on height and weight, and it is not gender specific. BMI does not measure percent of body fat.

BMI is determined by dividing a person's weight in kilograms by height in meters squared:

$$\frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

The BMI of an individual who weighs 160 lb and is 5′5″ tall is calculated as follows:

$$160 \text{ lb} \div 2.2 \text{ kg/lb} = 72.7 \text{ kg}$$

$$65 \text{ inches} \times 2.54 \text{ cm} = 165.1 \text{ cm} = 1.65 \text{ m}$$

$$(1.65 \text{ m})^2 = 2.72 \text{ m}^2$$

$$\text{BMI} = 72.7 \text{ kg} \div 2.72 \text{ m}^2 = 26.7 \text{ kg/m}^2$$

Table 28–3 illustrates calculated BMI values.

An expert panel convened by the National Heart, Lung, and Blood Institute (NHLBI) in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) further classified the categories for BMI (Table 28–4).

Determining BMI is inexpensive, simple, and quick, but it does have limitations. In very muscular adults, using BMI as a measurement tool may categorize them as "overweight" when they are fit and healthy. Another problem with using BMI is in adults who have lost muscle mass, such as the elderly. The tool may indicate they are in the "healthy" weight category when they may be at risk due to reduced nutritional reserves.

Waist Circumference

Waist circumference is positively correlated with abdominal fat content. It provides an acceptable measurement for assessing a patient's abdominal fat content and is most useful when the BMI is less than 35. Waist circumference is more predictive of illness risk than BMI after age 65 and in Asian-American populations. High risk for the development of hypertension, diabetes, and cardiovascular disease is associated in women with a waist circumference >35 inches (>88 cm) and in men > 40 inches (>102 cm).

Clinical Assessment of Obesity

The medical assessment of obesity should be done by the physician and include height, weight, and waist circumference. Medical examination should rule out other physiologic causes and assess overall risk status. In addition to a medical evaluation, a psychological assessment may be beneficial. This may include assessment for barriers to treatment including eating disorders, addictions, depression, and other mental disorders.

The nutritional assessment consists of an evaluation of current eating patterns including number and timing of meals and snacks, food preparation methods, and frequency of eating away from home. A history of weight and dieting should be assessed, along with weight changes after the age of 18. An assessment of motivation for weight loss and barriers to treatment including knowledge support systems, financial concerns, and physical limitations should be ascertained.

Physical activity level including type of exercise, duration, and intensity, as well as the patient's commitment to a program, should be determined.

Goals for Weight Loss and Management

The general goals of weight loss and management are: (1) prevent further weight gain; (2) reduce body weight; (3) maintain lost weight over a long term; and (4) reduce risk factors associated with obesity. Good evidence from randomized clinical trials indicates that the overweight and obese can successfully reduce health risks with a weight loss of 10% of baseline weight. With success, further weight loss can be attempted, if warranted, through further assessment.

Determination of Calorie Levels for Weight Loss

The focus of diet intervention for weight loss in overweight or obese patients is a low-calorie diet. No eating plan produces weight loss without a planned reduction in calories. This was demonstrated convincingly by the WHI.[39] A high-carbohydrate, low-fat diet taught without calorie reduction failed to produce sustained weight loss, thereby upending certain dogma that low-fat eating will "automatically" cause reduced calories and weight loss. Randomized trials suggest that weight loss at the rate of 1 to 2 lb per week is achievable by reducing calorie intake. Numerous methods to determine calorie needs for weight loss exist. One method for determining calorie needs is to calculate resting energy requirement by the Harris-Benedict Equation:[40]

For women: $\text{REE} = 655 + (9.56 \times \text{wt [kg]}) + (1.85 \times \text{Ht [cm]}) - (4.67 \times \text{age})$

For men: $\text{REE} = 66.5 + (13.75 \times \text{wt [kg]}) + (5.0 \times \text{ht [cm]}) - (6.8 \times \text{age})$

After determining resting energy requirement, add an activity factor and finally subtract kilocalories for weight loss.

Example:

Woman, 40 years old. Ht: 5′5″ (165 cm), Wt: 165 lb (75 kg), Activity Level: light

Step 1: REE using Harris-Benedict Equation

$\text{REE} = 655 + (9.56 \times 75) + (1.85 \times 165) - (4.67 \times 40)$

REE = 1491

Step 2: Add activity factor to REE and determine kilocalories for weight maintenance

Activity Level Description Multiplier

Bedrest: bedridden, sedentary = 1.0

Light: daily routine activities = 1.3

Moderate: regular exercise program in addition to daily activities = 1.5

Vigorous: heavy construction worker or athlete = 1.7

REE $1491 \times 1.3 = 1938$

Estimated calories for weight maintenance = 1938

Step 3: For weight loss, subtract 500 kcal* per day from kcal for weight maintenance

1938 calories - 500 kcal/day = 1438 kcal for weight loss of 1 lb/week

*3500 calories = 1 lb fat. By subtracting 500 calories/day from maintenance calories, patient can lose 1 lb/week (–500 kcal/day × 7 days/week = –3500 kcal or 1 lb fat).

Table 28–3 Body Mass Index Table

BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Height (inches)	Body Weight (pounds)																
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287

BMI	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Height (inches)	Body Weight (pounds)																		
58	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	243	250	257	263	270	277	284	291	297	304	311	318	324	338	338	345	351	358	365
70	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	272	280	288	295	203	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

To use the table, find the appropriate height in the left-hand column labeled "Height." Move across to a given weight. The number at the top of the column is the body mass index at that height and weight. Pounds have been rounded off.

Table 28–4 Classification of Overweight and Obesity by Body Mass Index

	Obesity Class	BMI (kg/m^2)
Underweight		<18.5
Normal		18.5-24.9
Overweight		25.0-29.9
Obesity	I	30.0-34.9
Obesity	II	35.0-39.9
Extreme obesity	III	≥40

BMI, body mass index.

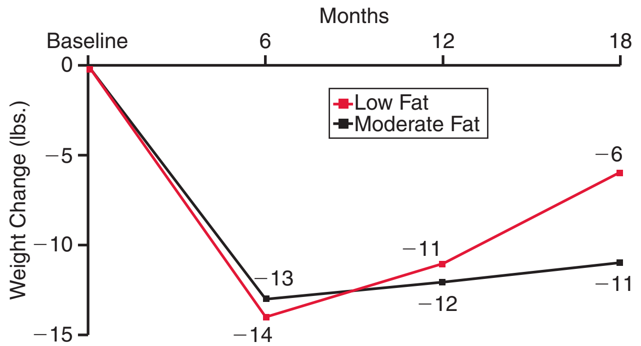

Figure 28–4 Comparison of a Mediterranean-style, high-unsaturated fat diet with a low-fat diet for weight loss. (Modified from McManus K, Antinoro L, Sacks F: A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. Int J Obesity 2001;25:1503-11.)

Another simpler method to determine the calorie level for a weight loss diet is to select a standard calorie level that has been used in many clinical trials on weight loss. Diets containing 1000 to 1200 kcal/day can be selected for most women; a diet between 1200 kcal/day and 1600 kcal/day can be chosen for men. The higher levels may be appropriate for women who weigh 165 lb or more or who exercise. A daily caloric deficit of 500 kcal will produce a weight loss of 1 lb per week. More gradual rates of weight loss can be achieved by more modest, sustained reduction of calories.

Macronutrient Contents of Diet Intervention for Weight Loss

Published clinical trials of long-term results for dietary treatment of obesity are limited. The debate continues as to the most effective macronutrient content of the diet to support weight loss and maintenance of lost weight.

Low-Fat versus Moderate-Fat Diet for Weight Loss

The conventional diet for weight loss is low in fat, which has a rational basis because fat is energy dense compared with carbohydrate. The low-fat hypothesis is that decreasing energy-dense fat in the diet will result in an overall reduction of calories. A meta-analysis of trials of low-fat diets showed a mean dietary reduction from 38% to 27% and resulted in a mean 3.2 kg weight loss.[41] These studies were mostly short term and have been challenged by other researchers, citing methodologic concerns for certain studies used in the analysis, including the often greater intensity of interventions in the low-fat compared with no-intervention control groups and the lack of randomized control groups.[42]

An alternative hypothesis to reducing fat to assist reduction in energy and thus weight loss is to reduce intake of all macronutrients but leave the usual dietary proportions of fat, carbohydrate, and protein unchanged. In some clinical trials with fully controlled dietary intake, the macronutrient composition did not affect the rate or total amount of weight loss over the short run.[43-45] The crucial factor for weight loss is reduction in calorie intake.

Nonetheless, it remains to be determined over the long run whether there is any relative advantage to diets that are reduced in fat (high carbohydrate) compared with those that are reduced in carbohydrate and higher in fat and protein. We compared these two approaches in a randomized trial and found that a moderate-fat diet based on the diets of southern Europe and the Mediterranean allowed for a greater variety of foods that are considered appetizing compared with a more bland, low-fat diet and had better long-term success.[46] In 101 overweight men and women, one half were instructed to eat a low-fat diet (20% calories from fat) and one half to eat a moderate-fat diet (35% calories from fat, mostly monounsaturated from peanut butter, nuts, olive and canola oils). After 18 months, only one in five study participants could stick to the low-fat diet, whereas more than one half stuck to the moderate-fat diet. Both groups lost an average of 11 pounds in the first 6 months. The moderate-fat group maintained significant weight loss for 18 months, whereas the low-fat group gained more than one half of it back (Fig. 28–4). After $2\frac{1}{2}$ years, the moderate-fat group still maintained this weight reduction. Surprisingly, those on the moderate-fat diet increased consumption of vegetables and fiber compared with the low-fat group. We attribute the success of a moderate-fat, energy-restricted diet to the fact that patients could include favorite foods if they carefully watched portion sizes. For example, they could use full-fat salad dressings, eat nuts for snacks, and sauté vegetables and meats.

High-Protein, Low-Carbohydrate Diets

A high-protein, low-carbohydrate diet for weight loss has been touted in the press. However, a review by Freedman, King, and Kennedy in 2001 concluded that a careful, scientific evaluation of these approaches to weight loss is necessary.[47] Subsequently, two studies reported that low-carbohydrate diets that increased protein or fat reduced body weight more than conventional low-fat diets over 6 to 12 months. However, at the 12-month point, the difference in weight loss lost statistical significance.[48,49]

Comparison of Popular Diets

Four diets popularly touted for weight loss in bestselling books were compared in a randomized trial lasting 1 year.[50] The diets were Ornish (very low fat, high carbohydrate), Weight Watchers (balanced calorie reduction), Zone (moderate reduction in carbohydrate, low glycemic index, increased protein and unsaturated fat), and Atkins (low carbohydrate, high

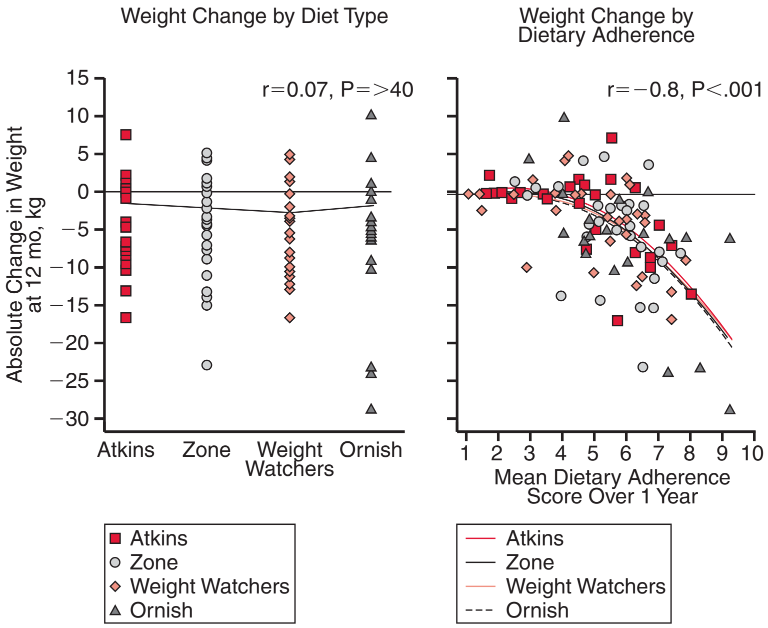

Figure 28–5 Comparison of popular weight loss diets. (Modified from Dansinger ML, Gleason JA, Griffith JL, et al: Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: A randomized trial. JAMA 2005;293:43-53.)

protein and fat). The diet instruction was minimal and based on the popular books; there was no sustained counseling or group support. Thus, the researchers mimicked one "real world" scenario that overweight people try. All four diets produced modest initial weight loss, which was not sustained (Fig. 28–5). Although there was no statistically significant difference in weight loss among the groups, the less extreme diets produced slightly better results (i.e., Weight Watchers and Zone). Interestingly, no matter what diet was assigned to a participant, good adherence produced better weight loss. Several participants in each group lost more than 25 lb at 1 year. A minority of overweight people can follow a weight loss diet with minimal support and sustain clinically meaningful weight loss at least to 1 year. However, as shown by other studies, adherence declines in the absence of continued supervision and support.

Healthy Eating Patterns

In determining appropriate diets to reduce risk of cardiovascular disease, one approach is to base food plans on healthy dietary patterns. A large body of epidemiologic and metabolic data indicates that a diet high in vegetables, fruit, legumes, and whole grains but low in animal foods, particularly red meat, provides a healthy alternative to typical U.S. and northern European diets that contain large amounts of meat, high-fat dairy products, highly refined carbohydrates, hydrogenated fats, and low amounts of vegetables and fruit.

Mediterranean Diet

One example of a healthful eating pattern is the Mediterranean diet. The traditional Mediterranean diet reflects food patterns typical of Crete, much of the rest of Greece, and southern Italy in the 1960s. The selection of this specific time and these geographic areas is based on evidence that adult life expectancy for populations in these areas was among the highest in the world and that rates of coronary heart disease, major cancers, and some other diet-related chronic diseases were among the lowest in the world.

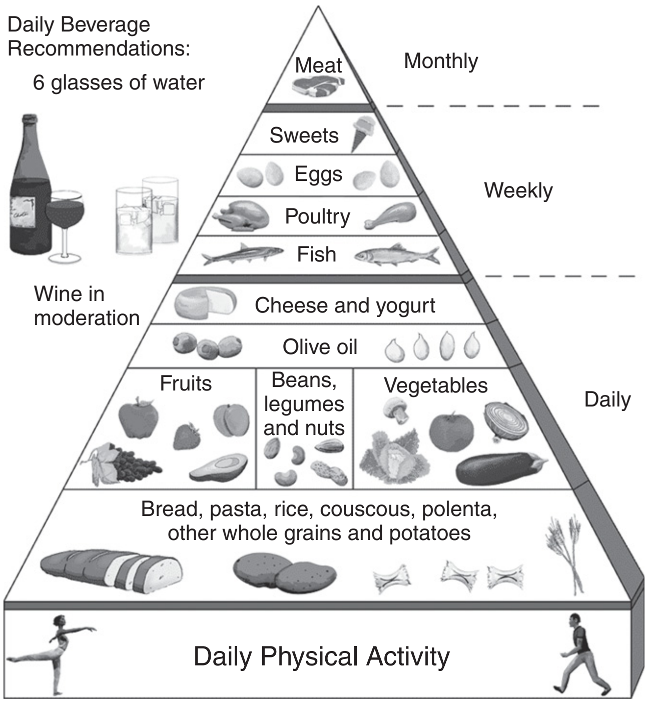

Figure 28–6 The traditional Mediterranean diet pyramid, developed in collaboration with the Nutrition Department of Harvard School of Public Health, the World Health Organization Regional Office for Europe, and the Oldways Preservation and Exchange Trust of Boston.

The Mediterranean diet of the early 1960s is described by the following broad characteristics:

- Abundance of plant foods that are minimally processed including vegetables, fruit, breads, beans, potatoes, nuts, seeds
- Olive oil as the principal fat
- Cheese and yogurt eaten daily in low to moderate amounts

- Fresh fruit as daily dessert—sweets containing sugar or honey eaten a few times per month
- Red meat eaten infrequently
- Wine in moderation with meals

In the traditional Mediterranean diet the percentage of calories from fat varies from 28% to 40% depending on the region. The majority of the fat is monounsaturated, with saturated fat being < 8% of total kilocalories.

The Mediterranean pyramid illustrated in Figure 28–6 is designed to convey a general sense of the relative proportions and frequency of consumption of foods that contribute to this overall dietary pattern. At the base of the pyramid, the diet features many different types of grains, bread, pasta, rice, bulgur (cracked wheat), and potatoes. Daily consumption of fruits, vegetables, beans, legumes, and nuts is encouraged, along with olive oil and moderate amounts of cheese and yogurt. Fish, poultry, and eggs are the main protein sources. Red meat is limited to a few times a month.

Table 28–5 Mediterranean-style Sample Menus

1500-Calorie Diet	2000-Calorie Diet
Breakfast 1 cup oatmeal 3/4 cup skim milk 2 Tbsp raisins 1 slice whole wheat toast 1 Tbsp peanut butter **Lunch** 3 oz skinless chicken breast 1 1/2 cups fresh spinach 1 Tbsp olive oil 1 Tbsp balsamic vinegar 2 whole wheat crackers 1 cup skim milk 1 medium orange **Snack** 1 oz almonds **Dinner** 4 oz broiled cod 1 baked sweet potato 5 mushrooms 1/2 cup asparagus 1 cup mixed greens 1 Tbsp. olive oil 1 Tbsp. vinegar 1/2 cup strawberries Calories: 1480 Protein: 90 g/24% Carbs: 165 g/45% Fat: 57 g/35% Sat: 9 g/5% Mono: 33 g/20% Poly: 10 g/6% Cholesterol: 119 mg Sodium: 940 mg Fiber: 28 g	**Breakfast** Egg white omelet with 2 egg whites and 1/8 cup each peppers, onions, mushrooms 1/2 Tbsp canola oil 1 slice whole wheat toast 3/4 cup blueberries 1/2 cup orange juice **Snack** 2 whole wheat crackers 1 Tbsp almond butter **Lunch** 1 cup vegetable soup, no added salt 3 oz turkey breast 2 slices whole wheat bread 1/4 cup avocado 3 slices tomato 1 cup 1% milk 1 apple **Snack** 1/2 cup carrots 1/8 cup hummus **Dinner** 4 oz broiled salmon 3/4 cup brown rice Mixed green salad 1/2 Tbsp olive oil 1 Tbsp vinegar Stir fry 1/2 cup broccoli and 1/2 cup cauliflower in 1/2 Tbsp olive oil **Snack** 3/4 cup low-fat vanilla yogurt 1 1/2 cups cantaloupe melon Calories: 2010 Protein: 107 g/21% Carbs: 240 g/48% Fat: 78 g/35% Sat: 15 g/7% Mono: 39 g/18% Poly: 17 g/8% Cholesterol: 163 mg Sodium: 1433 mg Fiber: 36 g

A Mediterranean-style diet can be successfully incorporated into the American diet using the main principles but substituting foods readily available and acceptable to the American palate. Table 28–5 illustrates a 1500-calorie meal plan and 2000-calorie meal plan that are patterned after the Mediterranean diet. The 1500-calorie meal plan can be used for a general weight loss plan for many adults, whereas a 2000-calorie meal plan is designed for weight maintenance. Table 28–6 shows an example of an alternative low-fat eating plan based on the DASH diet.[10]

Overall, the main objective in selecting healthful diets is to choose those that will not only reduce the risk of chronic disease but that are palatable and acceptable for long-term health. The Mediterranean-style diet and the DASH diet are approaches to eating that have proven to be acceptable and healthy. The OmniHeart study showed the superiority of a high unsaturated fat and protein diet on the basis of the principles established in DASH.[8] The OmniHeart unsaturated fat diet has strong similarities to the Mediterranean diet.

PHYSICAL ACTIVITY

Numerous scientific studies have demonstrated that physical activity prevents and treats many established risk factors including hypertension, insulin resistance and glucose intolerance, elevated triglyceride concentrations, low HDL cholesterol levels, and obesity.[51] The effect or benefit of exercise is influenced by the specific exercise, individual variation, and whether weight loss occurred. Physical activity can be an important adjunct to diet for obtaining and maintaining weight loss. The National Weight Control registry identified 3000 men and women who lost a minimum of 30 kg and maintained their weight loss for at least 1 year.[52] The average weight loss for these individuals was 30 kg, and the average amount of time that they maintained their lost weight was 5.5 years. Eighty-one percent of the participants reported physical activity. Women reported expending an average 2445 kcal per week, whereas men reported expending 3298 kcal per week. The physical activities most often recorded were walking, cycling, weight lifting, aerobics, running, and stair climbing.

Definition of Terms

Physical activity is defined as bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure.[52,53] Exercise is a subset of physical activity that is scheduled, repetitive, and has a goal of improving or maintaining physical fitness. Physical fitness includes cardiorespiratory fitness, muscle strength, body composition, and flexibility, comprising a set of attributes that people achieve and that relate to the ability to perform physical activity.

In describing physical activity or exercise, three components are assessed:

- Type—actual activity (i.e., walking, swimming, weight training)
- Duration—length of time
- Intensity—rate of energy expenditure

Recommendations for Primary Prevention

Type and Duration

The Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) recommend that individuals should engage in 30 minutes or more of moderate-intensity physical activity on most (preferably all) days of the week.[53] Patients should be encouraged to engage in a variety of physical activities and increase their activities as tolerated. Table 28–7 illustrates examples of a variety of moderate amounts of physical activity.

Intensity

The recommendation for maximum efficiency for cardiovascular health is to work at an intensity level equal to 65% to 85% of maximum heart rate (defined as Maximum Heart Rate = 220 – age of person).

Recommendations for Secondary Prevention

An American Heart Association consensus statement on preventing heart attack and death in patients with coronary disease suggested a minimum of 30 to 60 minutes of moderate-intensity activity 3 to 4 times weekly supplemented by an increase in daily lifestyle activities (e.g., using stairs, parking further from one's destination, taking walk breaks at work, performing household tasks); 5 to 6 hours a week were suggested for maximum benefits.[54]

Regular physical activity can improve heart function, reduce stress, and increase energy levels. The goal of 30 minutes of moderate-intensity activity most days of the week can be achieved by most people through a regular program of brisk walking. The public health challenge lies in promoting and supporting an active lifestyle early in life, which can be maintained throughout adulthood to reduce the risk of cardiovascular disease and other chronic diseases.

THE OVERALL EFFECT OF DIET AND LIFESTYLE

With full adherence, diet and exercise have strong potentials for major improvements in risk factors, dyslipidemia, high blood pressure, diabetes, and obesity. For example, strict vegetarians in Boston in the early 1970s showed very low cholesterol and blood pressure and near absence of overweight.[55] However, a more realistic approach is to simultaneously target more modest changes in several aspects of lifestyle. Together, these adjustments would be projected to reduce CHD markedly,[56] even if individual risk factors would be expected to change only mildly (Table 28–8).

Table 28–6 A Low-Fat Eating Plan Based on the DASH Diet, 2000 Calories a Day

Food Group	Daily Servings (except as noted)	Serving Sizes	Examples and Notes	Significance of Each Food Group to the DASH Eating Plan
Grains and grain products	7-8	1 slice bread 1 oz dry cereal* ½ cup cooked rice, pasta, or cereal	Whole wheat bread, English muffin, pita bread, bagel, cereals, grits, oatmeal, crackers, unsalted pretzels and popcorn	Major sources of energy and fiber
Vegetables	4-5	1 cup raw leafy vegetable ½ cup cooked vegetable 6 oz vegetable juice	Tomatoes, potatoes, carrots, green peas, squash, broccoli, turnip greens, collards, kale, spinach, artichokes, green beans, lima beans, sweet potatoes	Rich sources of potassium, magnesium, and fiber
Fruits	4-5	6 oz fruit juice 1 medium fruit ½ cup dried fruit ½ cup fresh, frozen, or canned fruit	Apricots, bananas, dates, grapes, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Low-fat or fat-free dairy foods	2-3	8 oz milk 1 cup yogurt 1½ oz cheese	Fat-free (skim) or low-fat (1%) milk, fat-free or low-fat buttermilk, fat-free or low-fat regular or frozen yogurt, low-fat and fat-free cheese	Major sources of calcium and protein
Meats, poultry, and fish	2 or fewer	3 oz cooked meats, poultry, or fish	Select only lean, trim away visible fats, broil, roast, or boil instead of frying, remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and dry beans	4-5/wk	⅓ cup or 1½ oz nuts 2 Tbsp or ½ oz seeds ½ cup cooked dry beans, peas	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils	Rich sources of magnesium, protein, and fiber
Fats and oils†	2-3	1 tsp soft margarine 1 Tbsp low-fat mayonnaise, 2 Tbsp light salad dressing 1 tsp vegetable oil	Soft margarine, low-fat mayonnaise, light salad dressing, vegetable oil (e.g., olive, corn, canola, safflower)	DASH has 27% of calories as fat including fat in or added to foods
Sweets	5/wk	1 Tbsp sugar 1 Tbsp jelly or jam ½ oz jelly beans 8 oz lemonade	Maple syrup, sugar, jelly, jam, fruit-flavored gelatin, jelly beans, hard candy, fruit punch, sorbet, ices	Sweets should be low in fat

*Equals ½-1¼ cups, depending on cereal type. Check the product's Nutrition Facts label.
†Fat content changes serving counts for fats and oils. For example: 1 Tbsp of regular salad dressing equals 1 serving; 1 Tbsp of a low-fat dressing equals ½ serving; 1 Tbsp of a fat-free dressing equals 0 servings.
The number of daily servings in a food group may vary from those listed, depending on your caloric needs. Use this chart to help you plan your menus or take it with you when you go to the store.
From the U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute.

Table 28–7 Examples of Moderate Amounts of Physical Activity*

Common Chores	Sports Activities	
Washing and waxing a car	Playing volleyball for 45-60 min	Less vigorous More time†
Washing windows or floors for 45-60 min	Playing touch football for 45 min	
Gardening for 30-45 min	Walking 1¾ miles in 35 min (20 min/mile)	↑
Wheeling self in wheelchair for 30-40 min	Basketball (shooting baskets) for 30 min	
Pushing a stroller 1½ miles in 30 min	Bicycling 5 miles in 30 min	
Raking leaves for 30 min	Dancing fast (social) for 30 min	
Walking 2 miles in 30 min (15 min/mile)	Water aerobics for 30 min	
Shoveling snow for 15 min	Swimming laps for 20 min	↓
Stairwalking for 15 min	Basketball (playing a game) for 15-20 min	More vigorous Less time
	Jumping rope for 15 min	
	Running 1½ miles in 15 min (15 min/mile)	

*A moderate amount of physical activity is roughly equivalent to physical activity that uses approximately 150 calories of energy per day, or 1000 calories per week.
†Some activities can be performed at various intensities; the suggested durations correspond to expected intensity of effort.
From the National Institutes of Health and National Heart, Lung, and Blood Institute: Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults. Evidence report. NIH publication #4083.

Table 28–8 Major Reduction in Cardiovascular Disease Risk by Making Modest Improvements in Lifestyle: The Nurses' Health Study

Primary Prevention of CVD: Five Attributes to Define Low Risk in the Nurses Health Study

1. Diet in upper 40% of population
   Good fat: Low saturated and trans fat, high polyunsaturated fat, high fish oil
   Good carbohydrates: Low-glycemic load, high fiber (whole grains)
   High folate (vegetables, fruit)
2. Not currently smoking
3. Moderate alcoholic beverage drinking (1 drink every other day to daily)
4. Regular exercise (½ hr daily, e.g., 2 miles/hr walking)
5. Body mass index < 25 kg/m^2 (optimal < 21 kg/m^2)

Three Low-Risk Attributes:
Good diet, no smoking, regular exercise
51% of coronary events and strokes could be avoided, but only 13% of nurses had this lifestyle

Four Low-Risk Attributes:
Good diet, no smoking, regular exercise, BMI < 25 kg/m^2
60% of events could be avoided; only 7% of nurses had these attributes

Five Low-Risk Attributes:
Above, plus moderate alcohol
74% CVD events, 82% coronary events in the population avoided, only 3% of nurses had these attributes

Modified from Stampfer MJ, Hu FB, Manson JE, et al: Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000;343:16-22.

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Chapter 29

The Steps Beyond Diet and Drug Therapy for Severe Hypercholesterolemia

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CHAPTER CONTENTS

A small subset of patients with hypercholesterolemia have an inadequate lipid-lowering response to maximum diet and drug treatment and should be considered for additional therapy to come as close as possible to the therapeutic targets of the National Cholesterol Education Program (NCEP).[1] Most candidates for treatment beyond diet and drugs are patients with familial hypercholesterolemia (FH) including all individuals with homozygous FH and patients with heterozygous FH who do not attain NCEP goals.

Treatment options alone or in combination include plasmapheresis, low-density lipoprotein (LDL) apheresis, portacaval shunt, liver transplantation, partial ileal bypass (PIB) surgery, and gene therapy. *Plasmapheresis* is a nonspecific, extracorporeal procedure that removes all plasma proteins including high-density lipoprotein (HDL) from the blood. A superior method that specifically lowers LDL cholesterol (LDL-C) in these patients is *LDL apheresis*. Methods for performing LDL apheresis include dextran sulfate cellulose adsorption, immunoadsorption, heparin-induced extracorporeal precipitation (HELP), and perfusion through whole blood–compatible columns. Time-averaged LDL lowering of 40% to 50% is achieved with weekly or every-other-week LDL apheresis therapy. The U.S. Food and Drug Administration (FDA) has approved LDL apheresis therapy for patients who, despite maximal tolerated diet and drug therapy, have an LDL-C concentration above 300 mg/dL without coronary artery disease (CAD) or an LDL-C concentration above 200 mg/dL with CAD. Dextran sulfate cellulose adsorption using the Liposorber System (Kaneka Pharma America) and HELP (B Braun) are the two systems available in the United States.

Surgical procedures for lowering LDL-C are more invasive than LDL apheresis and should only be considered if LDL-apheresis therapy does not provide adequate LDL-C lowering. *Portacaval shunts* have been used to achieve LDL-C lowering of about 40% as adjunctive therapy to LDL apheresis in patients with homozygous FH. *Liver transplantation* can achieve near normal LDL-C levels but is associated with considerable morbidity and the need for long-term immunosuppressive therapy. *Partial ileal bypass surgery* has slowed the progression of CAD, but it has appreciable morbidity rates and is not appropriate for patients with homozygous FH. *Gene transfer* has been used in a few patients with homozygous FH, with limited success. This therapy is not ready for widespread application in this patient population.

Increasing evidence indicates that LDL apheresis is beneficial in patients with refractory hypercholesterolemia and CAD and is clearly the therapy of choice for patients who require treatment beyond diet and drugs. The rapidity of clinical improvement in patients who receive LDL apheresis suggests mechanisms in addition to the regression of plaque. Whole blood–compatible systems for the performance of LDL apheresis will hopefully increase the acceptance of this therapy and decrease the cost. These systems have been used extensively in Europe but have not been introduced in the United States.

DEFINITION OF THE TARGET POPULATION

Because nondietary, nonpharmacologic therapy for hypercholesterolemia entails a major commitment from the patient and medical community, and in some instances substantial risk, clear guidelines for considering such therapy are necessary. All patients should have therapeutic lifestyle changes (TLC) instituted and be treated with maximum combination lipid-lowering drug therapy including (as tolerated) a reductase inhibitor, ezetemibe, and nicotinic acid. The FDA has approved LDL apheresis for patients with LDL-C concentrations substantially higher than levels recommended for initiation of lipid-lowering drug therapy.

Criteria for additional therapy should include the degree of LDL-C elevation and whether the patient has CAD or multiple risk factors for CAD. The FDA has approved LDL apheresis for the management of patients with CAD and LDL-C concentrations of more than 200 mg/dL or patients without CAD but an LDL-C concentration of more than 300 mg/dL. Table 29–1 summarizes this approach and incorporates selection criteria with those from the NCEP. Individuals with extremely high triglyceride concentrations or secondary causes of hypercholesterolemia are generally not candidates for the therapies described in this chapter.

Table 29–1 LDL-C Levels (mg/dL) and Initiation of Therapy

Categories	Diet + Drugs	LDL Apheresis + Diet/Drugs
Homozygous FH	All levels	All levels
High risk: CAD present or CAD equivalents	100 (70 optional)	200 (CAD only)
Moderate risk	130 or 160	300
Low risk	160 or 190	Not applicable

The recommendations of the third report of the National Cholesterol Education Program's Expert Panel (updated in 2004)[1] are combined with the recommendations for treating patients with severe hypercholesterolemia using LDL apheresis as approved by the FDA.
CAD, coronary artery disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

DESCRIPTION OF THE PATIENT POPULATION

Homozygous Familial Hypercholesterolemia

The clearest indication for nondietary, nondrug therapy is in patients with homozygous FH. This disorder is caused by the inheritance of two mutant genes at the LDL receptor locus. The clinical expression occurs in approximately 1 in 1 million persons. The defect in LDL receptor function causes a marked elevation in the plasma concentration of LDL-C, which typically exceeds 500 mg/dL but can reach as high as 1000 mg/dL.[2] HDL cholesterol (HDL-C) concentrations tend to be substantially below normal. Clinical features include the presence of xanthomas, severe aortic root disease including aortic stenosis, and the premature onset of CAD. Angina pectoris, myocardial infarction, or sudden death frequently occurs between the ages of 5 and 20 years. Mabuchi et al.[3] followed 10 patients with homozygous FH for a period of approximately 14 years. During that time, six of the patients died from sudden death or heart failure at an average age of 26. Similar observations were reported in patients from South Africa.[4]

The severity of the clinical expression depends to a great extent on the percentage of functioning LDL receptors. In the study by Goldstein and Brown[5] of 57 homozygotes, more than one fourth of receptor-absent patients died before the age of 25 compared with 1 of 26 individuals with residual LDL receptor activity. Because of the very high risk of premature CAD and the poor response to diet and drug therapy, all patients with homozygous FH require alternative therapy.

Patients with Low-Density Lipoprotein Cholesterol Concentrations of More Than 200 mg/dL and Coronary Artery Disease

The majority of patients in this group will have the heterozygous form of FH. This disorder has a prevalence of approximately 1 in 500 persons and is typically manifested by the occurrence of premature CAD by the fifth decade for men and the sixth decade for women. Clinically similar syndromes are produced by defects in the LDL receptor and defective apolipoprotein B (apoB) structure with impaired receptor binding. The presence of both CAD and elevated LDL concentrations is an important risk factor for subsequent coronary events, and therefore patients with CAD require intensive LDL-C concentration control. The reinfarction rate found in seven secondary prevention trials reviewed by Pekkanen et al.[6] was about 6% annually in contrast to a 1% to 2% rate of first infarction in four primary prevention trials. Trials in patients with marked hypercholesterolemia[7,8] have reported regression or a lower rate of progression of coronary lesions when the elevated LDL-C concentration is lowered with diet and drugs. Coupled with the impressive results from the trials that used the statins, a very persuasive case can be made for the aggressive treatment of subjects with familial hypercholesterolemia to achieve NCEP LDL-C targets.

Patients with Low-Density Lipoprotein Cholesterol Concentrations of More Than 300 mg/dL without Coronary Artery Disease

The decision of whether to use nondietary, nondrug therapy for primary prevention in asymptomatic adults is never as easy as it is in homozygotes. The risk of premature CAD is most apparent in patients with FH due to the presence of lifelong elevated LDL-C concentrations. In addition, the presence of risk factors other than LDL-C helps determine which patients are most likely to develop CAD. For example, a lipoprotein(a) [Lp(a)] concentration of more than 20 mg/dL has been recognized as an independent risk factor in patients with FH.[9,10] The use of noninvasive screening procedures for CAD, such as quantitation of coronary artery calcium, provides additional guidance for determining whether patients with elevated LDL-C will develop clinically significant disease.[11]

Based on current FDA guidelines, it is reasonable to consider nondietary, nondrug therapy for primary prevention in patients with an LDL-C concentration of more than 300 mg/dL despite diet and maximal tolerated lipid-lowering drug therapy.

EXTRACORPOREAL THERAPIES FOR THE TREATMENT OF SEVERE HYPERCHOLESTEROLEMIA

Background

Plasmapheresis and the more specific LDL apheresis procedures have provided safe and efficient methods for LDL lowering in patients with severe hypercholesterolemia. These techniques are available around the world and have become the most common mode of therapy for patients with refractory hypercholesterolemia. The first report of plasma exchange for FH was published by de Gennes et al.[12] in 1967. The procedure was performed manually and was too cumbersome for prolonged use. In 1975 Thompson et al.[13] described

the use of plasmapheresis with an automated cell separator to treat patients with homozygous FH. Plasmapheresis therapy has been shown to improve the survival of treated homozygotes compared with their untreated control siblings.[14]

The nonselectivity of plasmapheresis led to the development of LDL apheresis for the specific removal of apoB-containing lipoproteins from the blood. It is most useful in patients who respond incompletely to diet and lipid-lowering drug therapy because of drug intolerance or extremely high baseline LDL-C concentrations. The specific removal of apoB-containing lipoproteins was first described in 1976 by Lupien and colleagues[15] using heparin agarose beads. LDL apheresis has grown from a cumbersome laboratory procedure to a routine therapy with automated equipment. Methods for performing LDL apheresis include heparin-induced extracorporeal LDL precipitation (HELP),[16] columns that contain immobilized antibodies to LDL,[17] and columns that contain dextran sulfate cellulose.[18,19] Whole blood–compatible systems using columns containing either a modified polyacrylate gel (DALI System; Fresenius AG, St. Wendel, Germany)[20] or dextran sulfate (Liposorber-D; Kaneka Pharma, Osaka, Japan)[21] have been developed and have shown promise in initial investigations.

Studies to date have focused on the use of LDL apheresis in patients with severe hypercholesterolemia and CAD. The use and clinical acceptance of the procedure have increased worldwide, including approval in 1996 by the FDA.

Vascular Access

The primary consideration is achieving a sufficient blood flow rate for the patient. Fortunately, venous access from an antecubital fossa vein is most often sufficient for plasmapheresis and LDL apheresis because of the lower blood flow rates required (50 to 100 mL/min) compared with hemodialysis (400 mL/min). Should access from antecubital fossa veins provide insufficient blood flow, the placement of a fistula or graft may be necessary.

Anticoagulation

Some form of anticoagulation is necessary for all extracorporeal procedures. Heparin and acid citrate dextrose (ACD) are the anticoagulants most commonly used in extracorporeal therapies. Heparin is typically used for extracorporeal procedures that involve a membrane to separate whole blood into plasma and cells or in the whole blood–compatible system. Typically, a heparin bolus of approximately 20 to 50 U/kg is administered, followed by a continuous infusion of approximately 1000 U/h. Heparin is a very effective anticoagulant. However, its effects are still apparent several hours after completion of the procedure. ACD, which is also an effective anticoagulant, has the advantage of rapid metabolism and little residual effect after the procedure. Side effects due to ACD administration include symptoms of hypocalcemia, which may include perioral tingling; hypotension; or, very rarely, tetany.

Blood Separation

Most forms of LDL apheresis require the separation of blood into cells and plasma before the plasma is processed to specifically remove apoB-containing lipoproteins. Whole blood–compatible systems use direct adsorption of lipoproteins on columns and thereby eliminate the requirement for cell separation. For systems that require cell separation, either a membrane or centrifuge is used to separate blood into plasma and cellular elements. Membrane separation of blood is simpler and requires less extracorporeal volume, but it is less efficient than centrifugal techniques.

Frequency of Therapy, Lipid Lowering, and Volume of Blood Processed

Most patients are treated with LDL apheresis at a treatment frequency of approximately every 2 weeks. This is based on the rebound of the LDL-C, as well as the observation that most patients prefer to be treated no more often than every other week. At a treatment frequency of every 2 weeks there is usually a stepwise reduction in pretreatment LDL-C level until a new plateau is reached.

Cholesterol reduction can be quantified by measuring the achievement in either the acute or time-averaged lowering (Fig. 29–1). The acute lowering is the difference between preprocedure and postprocedure lipid values as a percent of the initial value and is a function of the amount of plasma or blood processed during a single treatment. Most plasmapheresis treatments process approximately a single plasma volume and achieve approximately 50% lipid lowering. Because nonspecific depletion of plasma proteins is not a problem, LDL apheresis procedures can process 1.5 to 2.0 plasma or blood volumes and reduce LDL-C concentrations acutely by 70% to 80%. For a blood flow of 50 to 80 mL/min, it takes about 3 hours to process 1.5 to 2.0 plasma or blood volumes.

Although acute lowering is helpful in determining treatment efficiency, the time-averaged lipid value is a better indicator of the lipid concentration to which the patient's arteries are exposed over an extended period. The time-averaged lowering is related to the treatment frequency and rate of rebound. The time-averaged lipid value is estimated by the formula 0.73 (pre LDL-C – post LDL-C) + post LDL-C or can

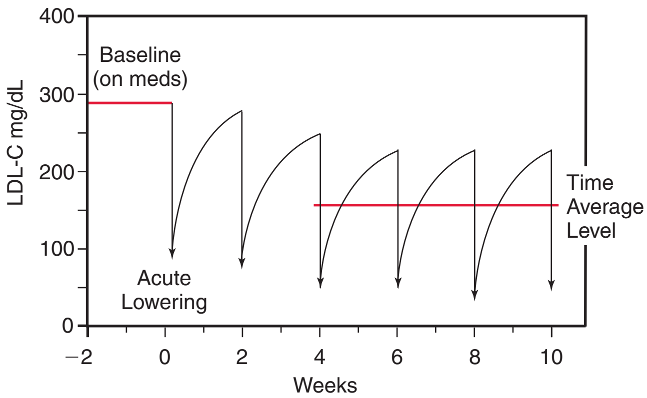

Figure 29–1 Acute and time average lowering of LDL-C for LDL apheresis treatments. The acute lowering is the difference in pretreatment and posttreatment levels as a percentage of the pretreatment level. The time average level is determined by measuring a "rebound" following a treatment.

be directly determined by measuring LDL-C daily after a treatment. The time-averaged LDL-C lowering is usually between 40% and 50%.

LDL apheresis has been reported to maintain or increase HDL-C concentrations over time.[22] The mechanism for this effect is unknown. The increase in HDL-C is seen most frequently in subjects with homozygous FH. In contrast, plasmapheresis lowers HDL-C through nonspecific depletion.

Plasmapheresis

Plasmapheresis was the original extracorporeal method for lowering LDL-C concentrations in individuals with FH. It has the advantages of being simple and safe. Unfortunately, HDL and other beneficial plasma proteins are also removed. This limitation makes plasmapheresis useful only in situations where LDL apheresis is not available. Because of the clear advantages of LDL apheresis compared with plasmapheresis, the remainder of this section is devoted to LDL apheresis.

Low-Density Lipoprotein Apheresis Using Dextran Sulfate Cellulose Columns

Dextran sulfate cellulose selectively binds apoB-containing lipoproteins on the basis of a charge attraction. Dextran sulfate cellulose columns were initially provided by the manufacturer as single, large-volume, nonregenerable columns that could be attached to any cell separator. Limited LDL-binding capacity resulted in the development of dual regenerable columns in a system that included a hollow-fiber primary cell separator (Fig. 29–2). Plasma is alternately perfused through each 150-mL column, permitting the regeneration of the off-line column with hypertonic sodium chloride solution. A computerized unit controls the process. The plasma, after passing through the adsorbent column, is recombined with the cells and returned to the patient. The advantage of this system is the almost unlimited LDL-binding capacity due to the on-line regeneration of the columns. The columns are discarded after each treatment.

Low-Density Lipoprotein Apheresis Using Immunoadsorption Columns

Immunoadsorption for the performance of LDL apheresis has been used to treat patients for approximately 25 years. Polyclonal monospecific or monoclonal antibodies to apoB are immobilized on a support, typically sepharose beads, and packed into glass columns. Each patient has two columns, which are reused during each procedure and reused from one procedure to the next because of the expense of making these columns. On-line regeneration of the columns is controlled by a column control unit (see Fig. 29–2). Typically, the columns are eluted with an acid solution, neutralized with a buffer solution, and then rinsed with saline. The procedure requires storage of the columns between treatments. All apoB-containing lipoproteins are removed [LDL, VLDL, and Lp(a)]. Because the columns are reused multiple times, they must be monitored for loss of activity that may occur after several months. In addition, sensitization of the patient to small quantities of shed antibody has been demonstrated.[23] Due to the cumbersome requirement of storing columns between uses, immunoadsorption LDL-apheresis is used less commonly than the other methods described in this chapter.

Low-Density Lipoprotein Apheresis Using Heparin-Induced Extracorporeal Low-Density Lipoprotein Precipitation

HELP-LDL apheresis specifically removes LDL, VLDL, and Lp(a) while minimally affecting HDL. HELP differs from other procedures in that it removes a substantial quantity of fibrinogen. The technique is based on the precipitation of positively charged LDL and other beta lipoproteins when heparin is added at a pH just above 5.0 (Fig. 29–3). A few

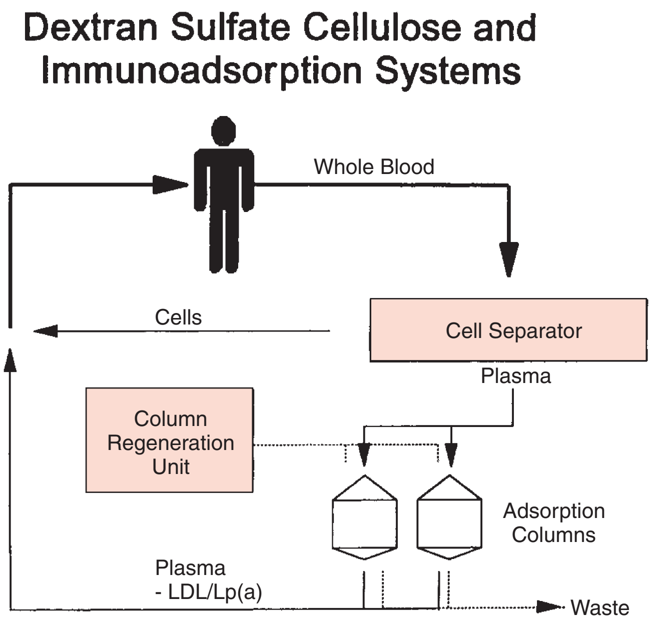

Figure 29–2 Schematic representation of dextran sulfate cellulose and immunoadsorption LDL apheresis systems.

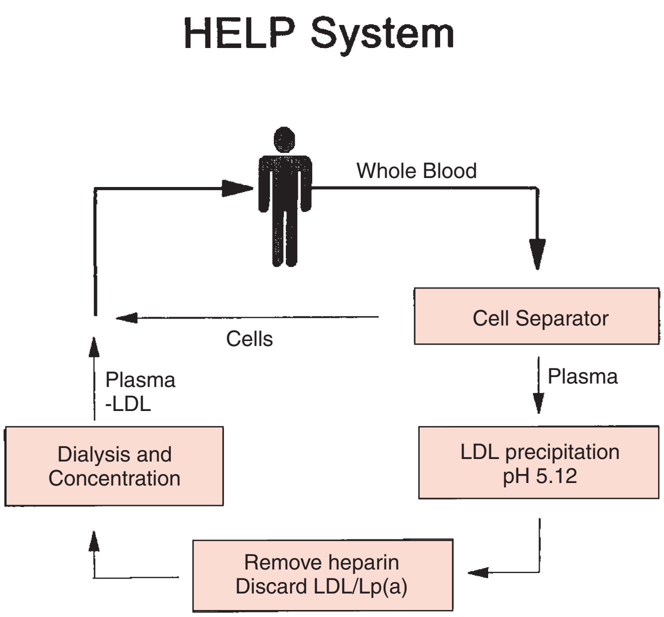

Figure 29–3 Schematic representation of the HELP-LDL apheresis system.

other plasma proteins precipitate to some extent with heparin, most notably fibrinogen. An anion exchange column removes excess heparin. The plasma is treated with bicarbonate dialysis and ultrafiltration to return pH to normal and remove excess fluid. The entire process is controlled by a microprocessor.

Low-Density Lipoprotein Apheresis Using Whole Blood–Compatible Systems

An important advance in the technology of performing LDL apheresis has been the development of whole blood–compatible systems. Potential cost savings and simplicity of use make a whole blood–compatible system very attractive for the performance of LDL apheresis. Two systems are currently available—The DALI System and Liposorber-D (Fig. 29–4). A comparison between the whole blood compatible systems and classic techniques for performing LDL apheresis is shown in Table 29–2. The DALI system uses a modified polyacrylate gel immobilized on a solid support. The mechanism of apoB binding is an electrostatic interaction between the positive charges of the apoB and the negatively charged carbohydrate moieties on the polyanionic gel.

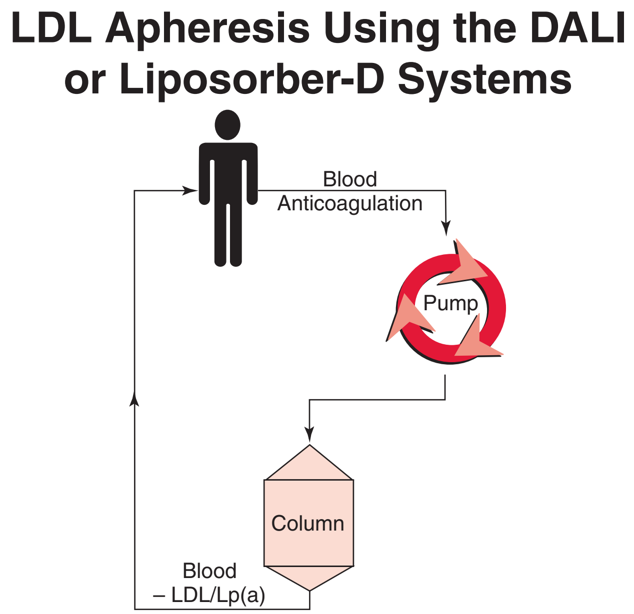

Figure 29–4 Schematic representation of the DALI and Liposorber-D whole blood–compatible LDL apheresis systems.

The initial two-center pilot study[20] reported on 12 hypercholesterolemic patients treated once each with columns containing 400 mL polyacrylate gel. No side effects were observed. A follow-up study reported the use of this technology in the therapy of three hypercholesterolemic subjects with atherosclerosis.[24] The acute reduction in lipids was 66% for LDL-C, 63% for Lp(a), and 29% for triglycerides. HDL and fibrinogen were lowered minimally. No clinically significant adverse events occurred, and the changes in biochemical and hematologic parameters were minor. The authors noted that the setup time for the procedure was only 30 minutes as opposed to 1 hour or more for other forms of LDL apheresis. The Liposorber-D system is based on binding of apo-B containing lipoproteins to dextran sulfate. The matrix has been modified to permit the safe interaction between whole blood and the column. The clinical experience in 10 subjects treated with this system was recently reported.[21] LDL cholesterol reduction was 62%. No significant side effects were observed. Whole blood–compatible systems are extremely promising despite the unknown long-term effects of whole blood interactions with the column. This form of LDL apheresis will hopefully be less expensive than established methods.

Risks of Low-Density Lipoprotein Apheresis

Adverse reactions due to LDL apheresis have been few. The extracorporeal volume is well tolerated even in patients with severe CAD. Hypotension requiring infusion of saline occurs in less than 5% of treatments. Unusual side effects include angina, hemolysis, and allergic or anaphylactic reactions. In immunoadsorption treatments, possible causes of adverse reactions include complement activation and sensitization of the patient to column constituents. An anaphylactoid reaction during dextran sulfate LDL apheresis has been described in patients taking angiotensin-converting enzyme (ACE) inhibitors.[25] The mechanism is related to release of bradykinin during LDL apheresis with concomitant decreased degradation of kinins by ACE inhibitors. The DALI system also activates the kallikrein-kinin system. Patients taking a short-acting ACE inhibitor should not take their ACE inhibitor for at least 24 hours before LDL apheresis therapy, whereas patients taking a long-acting ACE inhibitor should not take their medication for at least 48 hours before therapy. We have found that a better approach is to switch patients from ACE inhibitors to angiotensin II receptor blocking drugs before the initiation of LDL apheresis. Treatment with immunoadsorption

Table 29–2 Comparison of LDL-Apheresis Methods

Method	DALI	Liposorber-D	Liposorber	Immunoadsorption	HELP
Set-up time (approximate)	30 min	30 min	60 min	60 min	60 min
Reusable	No	No	No	Yes	No
Plasma/blood	Whole blood	Whole blood	Plasma	Plasma	Plasma
Principle	Polyacrylate	Dextran sulfate	Dextran sulfate	Antibodies	Heparin precipitation
Experience	Moderate	Limited	Extensive	Extensive	Extensive

Systems: DALI, direct adsorption of lipoproteins; Liposorber-D, dextran sulfate–based whole blood perfusion system; Liposorber, dextran sulfate cellulose column–based system; Immunoadsorption, low-density lipoprotein apheresis using columns containing immobilized antibodies on a support; HELP, heparin-induced extracorporeal low-density lipoprotein precipitation.

LDL apheresis or the HELP system are not associated with this clinical problem.

Benefits of Low-Density Lipoprotein Apheresis

Regression of tendon xanthoma and improvement in CAD have been demonstrated in patients with severe hypercholesterolemia when the LDL-C concentration is lowered through LDL apheresis protocols. In the LDL Apheresis Regression Study (LARS),[26] angiographic evidence for regression of CAD was observed in 10 of 30 patients treated with LDL apheresis and lipid-lowering drugs despite a baseline LDL concentration of 311 mg/dL. The HELP-LDL Apheresis Multicenter Study[27] was a 2-year investigation in 51 patients treated with weekly LDL apheresis and lipid-lowering drugs. Computer-assisted analysis of paired angiograms from 33 evaluable patients revealed that 23 patients had regression, 1 had little change, and 9 patients had progression. The German Multicenter LDL Apheresis Trial[28] was a four-center, 3-year prospective trial of 32 patients with FH. All patients who had symptomatic CAD experienced improvements in their symptoms by the end of the study. Improvement in electrocardiographic stress testing was demonstrated in 17 patients. Analysis of the paired angiograms did not reveal regression of disease, although definite progression of disease was observed in only five patients over 3 years.

An important study was the LDL-Apheresis Atherosclerosis Regression Study (LAARS), a prospective 2-year randomized one-center study in men with hypercholesterolemia and CAD.[29] This trial demonstrated that the addition of biweekly LDL apheresis to treatment with simvastatin improved regional myocardial perfusion and decreased myocardial ischemia. Of interest, there was little change in the coronary angiograms. Peripheral vascular disease was also found to improve in LAARS, as shown by standardized techniques including B-mode ultrasound.

Studies using intravascular ultrasound demonstrate that the angiogram may miss changes that occur in the blood vessel wall rather than the blood vessel lumen. The Low-Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial (LACMART) used intravascular ultrasound to compare change in coronary artery disease in 18 patients with familial hypercholesterolemia randomized to 1 year of either drug therapy or LDL apheresis combined with drug therapy.[30] Favorable changes in coronary artery minimal luminal diameter and plaque burden were observed in subjects receiving LDL apheresis plus drug compared with subjects receiving drug alone.

LDL apheresis with the HELP system has also been used to treat a patient with hypercholesterolemia and progression of CAD after heart transplantion.[31] The patient had clinical improvement documented by coronary angiography. LDL apheresis with the Liposorber system decreased the rate of restenosis in patients with elevated Lp(a) concentrations who had undergone coronary angioplasty.[32]

A multicenter study in the United States demonstrated the ability of LDL apheresis to decrease the number of clinical events in patients with CAD.[33] The rate of clinical events per 1000 patient-months decreased from 9.14 for the 5-year period before the initiation of LDL apheresis to 4.72 during the LDL apheresis period ($P = 0.037$). An analysis of data from the U.S. LDL Apheresis Registry established at the time of FDA approval of LDL apheresis confirmed the decrease in clinical events in a larger number of patients. In 1998 Mabuchi et al.[34] reported long-term outcome data in a study of 130 heterozygous FH patients with CAD. LDL apheresis combined with drug therapy produced a reduction in coronary events during a 6-year period. The rate of coronary events in the LDL apheresis-plus-drug group (n = 87) was 10% compared with 36% in the drug-alone group (n = 43).

Benefits of Low-Density Lipoprotein Apheresis Beyond Reducing Low-Density Lipoprotein Concentrations

The rapidity of clinical responses in some patients receiving LDL apheresis has suggested effects in addition to LDL lowering and regression of plaque. A number of mechanisms are likely for this observation including (1) decreased blood viscosity with improved blood rheology[35]; (2) improved coronary microcirculation; (3) lowered oxidized LDL concentrations[36]; (4) the removal of small, dense LDL particles; and (5) downregulation of leukocyte and endothelial adhesion molecules.[37] Tamai et al[36] measured forearm blood flow while infusing acetylcholine before and after a single LDL apheresis treatment and found that vasodilation responses were significantly augmented. The reductions in LDL and oxidized LDL correlated with the increase in acetylcholine-induced vasodilation.

SURGICAL PROCEDURES

Portacaval Shunt

Background

In 1963 a portacaval diversion was used to treat a child with a glycogen storage disease.[38] The observation by Starzl et al.[39] that the hyperlipidemia observed in these patients was improved by portacaval shunting provided the basis for using the procedure, starting in 1973, to treat severe forms of hypercholesterolemia.[40] The majority of reported cases had homozygous FH,[41,42,43] with a few cases of severe heterozygous FH also reported.

Technique

With the exception of the earliest procedures, all patients received end-to-side portacaval anastomoses. The portal vein is severed and connected with sutures to the suprarenal inferior vena cava, causing portal blood to completely bypass the liver (Fig. 29–5). The liver retains arterial flow through the hepatic artery.

Cholesterol Lowering

Table 29–3 shows the consistent and substantial total cholesterol and LDL-C lowering in 17 LDL receptor-negative patients. Nine were from Starzl's series,[42] and eight additional patients were treated at our center, of whom four had shunt surgery at the University of Pittsburgh and metabolic studies at the Rockefeller University. The average reductions in cho-

lesterol for the two groups were very similar, 37% and 42%, respectively, with all except one subject showing a better than 25% reduction. The decline in cholesterol began the week after surgery, with a plateau reached at about 6 months, and was sustained in all patients for the period of follow-up (4 months to 21 years), with no evidence of shunt closure. The HDL concentrations increased in every subject in our series (average of 36%) but had a more variable response in Starzl's series. Triglyceride concentrations, usually normal in this disease, decreased in all subjects except one. Two patients with heterozygous FH reported by Starzl et al.[42] had a similar lipid response to portacaval shunting. Less successful lowering was reported when the shunt was not fully patent or when collateral vessels were not completely tied off at the time of surgery.[43]

The hypocholesterolemic effect is coincidental with a marked decrease in cholesterol, bile acid, and LDL apoB synthesis and a decrease in cholesterol pool size.[44,45] Exogenous cholesterol absorption remains unchanged. In a 21-year-old receptor-negative homozygote patient, a liver biopsy 3 months after portacaval shunt revealed a marked decrease in the size of the hepatocytes, content of lipid and glycogen, and both rough and smooth endoplasmic reticula.[46] HMG-CoA reductase activity was decreased by 56%, and receptor-independent binding of LDL was significantly increased. These changes in the liver after a portacaval shunt have been attributed to loss of the first pass of portal blood containing high concentrations of hepatotropic substances, with the most important being insulin.[40] Many other synthetic functions of the liver, however, including the production of albumin, are unaffected.

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Please refer to the printed publication.

Figure 29–5 End-to-side portacaval shunt. (From Zuidema GD, Cameron JL, Zeppa R: Portal hypertension. In Nora PF (ed): Operative Surgery: Principles and Techniques. Philadelphia, Lea & Febiger, 1980, p 694.

Risks and Benefits

Portacaval shunt surgery is generally well tolerated even in patients with symptomatic cardiac disease. The patient is typically discharged 3 to 4 days after surgery, with a single surgical follow-up visit 2 weeks later. In two of the larger series combined, 1 perioperative death occurred in 25 patients, most of whom had valvular or coronary disease at the time of surgery.[42,43] An NIH-sponsored registry of 45 shunted hypercholesterolemic patients reported three deaths within 30 days of surgery.[41]

The most feared adverse effect of the shunt is encephalopathy and intellectual deterioration. However, except for a single reported case of a brief period of coma 9 months after surgery in a 2 year-old child, there have been no reports of encephalopathy.[41,42,43] At our center, an adult heterozygote and four prepubertal homozygotes tested before and 1.5 to 2.5 years after surgery showed no changes in electroencephalographic, intelligence quotient, and other psychological parameters. One of these patients, age 25, who underwent portacaval shunt surgery at age 4, is a fully employed, healthy college graduate. Another patient with severe aortic stenosis developed a mild tremor 4.5 years after shunt surgery and then died suddenly of a myocardial infarction. At autopsy, he had mild cerebroventricular dilation and slightly thickened leptomeninges but no astrocyte proliferation or other changes typical of hepatic encephalopathy.

For the follow-up periods reported (generally <5 years), there has been no evidence of progressive hepatic dysfunction. However, mild liver enzyme abnormalities and elevated

Table 29–3 Effect of Portacaval Shunt Surgery on Lipid Profiles in Familial Homozygous Hypercholesterolemia

Average % Change [range]

	Starzl		Rogosin Institute	
Total cholesterol	–37	(–23 to –55)	–42	(–31 to –50)
LDL cholesterol	–36	(–21 to –44)	–43	(–36 to –50)
HDL cholesterol	–22	(–66 to +26)	+36	(+15 to +50)
Triglycerides	–19	(–63 to +80)	–35	(–12 to –63)

Data were obtained from 17 LDL receptor–negative patients before and at least 4 mo after shunting performed at ages 2-21. Nine patients were reported in Starzl TE, Chase HP, Ahrens EH Jr, et al: Portacaval shunt in patients with familial hypercholesterolemia. Ann Surg 1983;198:273-83, and the data from 8 patients are from our unpublished observations.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

ammonia concentrations occur.[39,42] We have also consistently seen a slight prolongation of prothrombin time and partial thromboplastin time and a reduction in several clotting factors after surgery, which thus far have not resulted in any clinically significant bleeding. The acceleration in growth in children after shunting has been attributed to improved health.[42] However, portacaval shunt surgery may alter growth by increasing blood levels of adrenal androgens. In two of our prepubertal male patients, rapid growth was associated with accelerated bone age; increased serum testosterone; and, in one case, precocious adrenarche that was successfully treated with hydrocortisone. One of our female patients also became amenorrheic with a high testosterone level, ovarian cysts, and other characteristics of the polycystic ovary syndrome after shunt surgery and was hyperinsulinemic after an oral but not intravenous glucose challenge. Case reports of increased serum testosterone have also occurred after shunting in post-menarchal females, although a survey of pituitary and thyroid function including testosterone before and 4 to 6 months after surgery failed to show changes in six homozygotes.[47] Clearly, the long-term effects of portacaval shunt surgery on liver function, growth, and sexual maturation need to be much better defined.

The follow-up of patients undergoing portacaval shunting has demonstrated that xanthomas regress and disease stabilization and improvement are possible. Starzl et al.[42] reported two cases of improved aortic stenosis, as evidenced by decreased aortic gradients 13 and 16 months after surgery. Coronary angiography in five patients from 7 months to 7 years after the procedure suggested improvement in one patient and disease stabilization in two. Disease stabilization over a similar time period for two patients who had also undergone coronary artery bypass graft surgery has also been reported.[48] However, coronary disease will often progress unless this surgery is combined with LDL apheresis to lower LDL-C sufficiently. We have treated an LDL receptor–negative patient without cardiovascular disease with a portacaval shunt at age 4 and LDL apheresis from the age of 6. He has continued biweekly LDL apheresis treatment for 19 years and has a time-averaged LDL-C concentration of 180 mg/dL, with no evidence of coronary or significant valvular disease.

Treatment Guidelines

Because of the uncertain, long-term hepatic and endocrine effects, portacaval shunt surgery should be reserved as adjunct therapy to LDL apheresis in the patient with an elevated LDL and significant cardiovascular disease. Portacaval shunt surgery is also an option for young children with significant valvular or coronary disease, or both, who are not large enough for treatment with LDL apheresis. The surgery should be performed before major clinical deterioration, at a time when the benefits of the surgery outweigh the risks of the operative procedure.

Liver Transplantation

Background

The first liver transplantation for homozygous FH was performed in a 6-year-old patient by Starzl in 1984.[49,50-52] Because of diffuse coronary atherosclerosis, heart transplantation was performed at the same time. Table 29–4 illustrates the dramatic increase in hepatic LDL clearance, decrease in LDL production, and plasma levels of LDL-cholesterol in this patient. Further LDL cholesterol lowering into the normal range was achieved with the addition of a statin. Similar results summarized in Table 29–5 have been reported for five other homozygous FH patients treated with combined heart-liver transplants (ages 6 to 46 years) and for 13 patients with liver-only transplants (ages 2.5 to 21 years). The longest follow-up has been 9 years after combined heart-liver transplant[53,54,55] and 13 years after liver-only transplant[56] (personal communication); nine patients were followed at least 4 years. Three patients previously had ileal bypass surgery or portacaval shunts, or both, that made the liver transplant surgery more technically difficult.[57,58] Four patients, ages $2\frac{1}{2}$ to 6, had normal coronaries and aortic valves at the time of liver transplant and were well 0.5 to 4 years later.[59-62] Two of these young patients each received a transplant from a heterozygote parent and thus required statin therapy to lower the LDL cholesterol further.[60,62]

Cholesterol Lowering

After transplantation, most homozygous FH patients met or exceeded NCEP guidelines (TC <225 mg/dL) within a few weeks of transplant. These excellent results were sustained over time and occurred despite treatment with steroids, cyclosporin, and other immunosuppressant agents that may increase lipid concentrations. Only four received additional therapy with statins. Lp(a) has also been reported to decrease,[63] and HDL-C may increase.

Risks and Benefits

Of the nine homozygous FH patients treated with heart-liver transplant, one died within a month of surgery after repeat heart-liver transplantation,[57] another died 4 years later of noncompliance with immunotherapy[59] (personal communication), and a third died 7 years later probably due to chronic rejection of the heart.[64] Of the 13 patients with liver-only transplants, just one death occurred from a myocardial infarction 2 years after surgery.[65] Four patients required retransplant of the liver due to infectious hepatitis, hepatic artery thrombosis, chronic hepatic rejection, or myocardial infarction. One 13-year-old patient had a myocardial infarction immediately after liver transplant surgery and required coronary artery bypass grafting.[66] Four reports documented by angiography the absence of progression[59,63,66,67] and regression[68] in coronary artery disease. Growth and development occurred normally.

Treatment Guidelines

For the treatment of some homozygous FH patients, the benefits of the sizable and sustained reduction in the level of LDL cholesterol may outweigh the risks of transplant surgery, chronic rejection, and immunosuppressive therapy. In practical terms, liver transplantation is often not a treatment option because waiting lists are long for cadaver livers and many family members including both parents have partial

Table 29–4 Response to Liver Transplant and Lovastatin in a Patient with Homozygous Familial Hypercholesterolemia

	Baseline	Liver Transplant	Transplant + Lovastatin
Total cholesterol (mg/dL)	1079	302	171
LDL-C (mg/dL)	988	184	107
Triglyceride (mg/dL)	238	218	121
HDL-C (mg/dL)	35	41	39
Catabolic rate (pools/d)	0.12	0.31	0.30
Production (mg/kg/d)	36.4	16.7	10.9

From East C, Grundy SM, Bilheimer DW: Normal cholesterol levels with lovastatin (mevinolin) therapy in a child with homozygous familial hypercholesterolemia following liver transplantation. JAMA 1986;256:2843-48.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 29–5 Summary of Liver and Heart-Liver Transplantation for the Treatment of Homozygous Familial Hypercholesterolemia

	Liver Transplant	Heart-Liver Transplant
Number of subjects	13	6
Date of surgery	1985-2002	1984-1996
Age at surgery (yr)	2.5-21	6-46
Length of follow-up (yr)	0.5-13	0.5-9
Preoperative cholesterol (mg/dL)	480-1170	700-1160
Follow-up cholesterol (mg/dL)	116-254	174-221
Number of deaths	1 (at 2 yr)	3 (at 1 mo, 4 and 7 yr)
Number with retransplants	2	2
Number on statins	2	2

Data from references 49-68. Includes 3 patients with prior ileal bypass or portacaval shunt surgery, or both. Follow-up cholesterol data include 2 patients with heterozygote living–related donors.

defects of the LDL receptor and therefore are not optimal liver donors. Until there is more information about the long-term health of liver transplant patients, liver transplantation should be reserved for the homozygous FH patient with established cardiovascular disease or evidence of progression despite maximum treatment with LDL-apheresis and drugs.

The liver transplant surgery should be performed before the vascular or valvular disease, or both, progresses to an unstable state. In the case of life-threatening heart failure, the liver and heart transplant can be combined, but with increased surgical complications and mortality.

Partial Ileal Bypass

Background

The PIB surgical procedure was introduced for the management of hypercholesterolemia in 1963.[69] More than 600 PIB procedures have been performed for this purpose.[70,71] The procedure lowers serum cholesterol by increasing the fecal loss of cholesterol and bile acids. A reduction in the absorption of cholesterol and bile acids stimulates an increase in hepatic cholesterol synthesis but also LDL receptor expression and the hepatic conversion of cholesterol to replenish the depleted bile-acid reservoir.[72] Its use has been best evaluated in patients with heterozygous FH. The lack of LDL receptors in homozygous FH may explain the minimal clinical response to PIB in this disorder.[73,74]

Technique

The PIB operation for lowering cholesterol bypasses the distal 200 cm or the distal third of the small intestine, whichever is greater. The ileum is divided, the proximal segment is anastomosed to the side of the cecum, and the closed distal segment is tacked to the cecum. This procedure is different from the weight-losing procedure, which includes a more extensive 90% jejunal-ileal bypass.

Cholesterol Lowering

The Program on the Surgical Control of the Hyperlipidemias (POSCH)[70,75,76] randomized 421 middle-aged survivors of a myocardial infarction and with an LDL cholesterol of at least 140 mg/dL to cholesterol-lowering therapy with PIB. The study began in 1975 before the general availability of HMG-CoA reductase inhibitors. At 5 years, surgery resulted in a 23% decrease in total cholesterol, a 38% decrease in LDL-C, a 4% increase in HDL-C, and a 20% increase in triglycerides. The responses were generally sustained for as long as surgical bypass was maintained (up to 20 years). Synergy with statins has been reported.[71]

Risks and Benefits

The operative and perioperative mortality rates are extremely low. The principal side effect of PIB surgery is more frequent and looser stools. During the first 5 years of follow-up, 6% to 8% of the surgically treated patients in the POSCH trial reported watery or frothy stools compared with 0% to 1% of controls. The average weight loss was 5.3 kg. Of PIB patients, 13.5% had at least one symptom of bowel obstruction (the majority occurred within the first year), but only 3.6% required surgical intervention. Surgically treated patients had a higher incidence of kidney stones (4% versus 0.7% per year) and gallstones (17% versus 5%). Twenty-three (6%) of the POSCH patients underwent reversal of surgery between 2 and 11 years after surgery, usually because of diarrhea.

The POSCH trial demonstrated that lipid lowering by PIB resulted in less progression and regression of coronary and peripheral vascular atherosclerosis compared with controls at 3, 5, 7, and 10 years after surgery.[75] Overall mortality was reduced by 20% at 18 years of follow-up.[76] There was no increase in colorectal cancer.

Gene Therapy

Background

Progress in molecular biology has provided hope for fixing the basic error in patients with severe FH through a technique called *gene transfer* (see Chapter 3). The foundation for this work was established by Goldstein and Brown,[5] who demonstrated that in the majority of patients, an absent or a defective LDL receptor was the cause of the marked elevation in LDL-C. Gene therapy would provide a normal copy of the missing or defective gene for the LDL receptor. In a single therapeutic trial, liver tissue from 5 patients, ages 7 to 41, with homozygous FH was harvested; the normal LDL receptor gene transduced with a recombinant retrovirus into the cells; and the hepatocytes reinfused into each patient through the mesenteric vein.[77] At 4 months a liver biopsy and in situ hybridization using an RNA probe specific for the recombinant-derived LDL receptor transcript revealed relatively few hepatocytes containing the transgene. In addition, only two of five subjects showed significant reductions in LDL-C (19% and 23%).

Although this attempt demonstrated the feasibility of correcting the LDL receptor abnormality in a limited number of hepatocytes, it was clear that better methods of gene therapy were necessary to correct this disorder. More appealing is intravenous delivery of the gene targeted specifically to the intact liver. Efficient and safe in vivo gene transfer has been difficult primarily because hepatocytes rarely divide without a stimulus, such as a partial hepatic resection. Fortunately, other viral vectors and nonviral approaches for gene transfer may be applicable. Adenoviruses have the capability of transducing genes into hepatocytes that are not dividing but may induce an immune response against the virus. Marked and sustained reduction of LDL cholesterol and atherosclerosis has been recently achieved in LDL receptor–deficient mice injected intravenously with novel, less immunogenic, liver-specific viral vectors, such as an adeno-associated virus from a nonhuman primate[78] and a helper-dependent adenovirus depleted of immunogenic viral genes.[79] Similar success has been obtained with a lentivirus vector in the Watanabe Heritable Hyperlipidemic (WHHL) rabbit model.[80]

CONCLUSIONS AND RECOMMENDATIONS FOR THERAPY

The treatment of patients with hypercholesterolemia who respond inadequately to diet and lipid-lowering drug therapy remains a challenge. Patients with homozygous FH are the clearest candidates for additional therapy because of their poor response to standard treatments. LDL apheresis has been the most commonly used treatment modality and is the safest alternative. This therapy should be initiated as early as possible and technically feasible. Generally age 5 or body weight of 15 kg is the lower limit because of difficulties with vascular access and the approximately 200 mL of blood in the extracorporeal circuit. An additional 10% to 20% cholesterol lowering can be achieved with the addition of atorvastatin and ezetimibe. Liver transplantation (and combined heart-liver transplantation when heart function is severely impaired) should be considered if LDL apheresis plus medication is technically difficult or inadequate at controlling the LDL-C concentration and progression of atherosclerosis. When a liver transplant, often limited by donor availability, is unfeasible or unacceptable, combination therapy with portacaval shunting, LDL apheresis, and medication may lower LDL-C sufficiently to prevent progression of atherosclerosis. Plasmapheresis is an alternative when LDL apheresis is not available. Gene therapy is not in use in clinical trials at present but is in active study in animal models.

The most frequent indication for LDL apheresis is the adult patient with heterozygous FH who has CAD and LDL-C concentrations higher than 200 mg/dL despite maximal diet and drug therapy. The use of nondietary, nonpharmacologic therapy as primary prevention in heterozygous patients without CAD but with LDL-C concentrations of more than 300 mg/dL and who are inadequately responsive to standard measures is more problematic. The standard risk factors should be used to segregate a small subset of individuals at the highest risk for the development of atherosclerosis in whom additional therapy is reasonable. The best alternative is LDL apheresis, but if this is not possible, PIB is also an option. Particularly for these patients, the decision to provide these therapies must be individualized.

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Hypertension

Chapter 30

Initial Evaluation and Approach to the Patient with Hypertension

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CHAPTER CONTENTS

An estimated 59 million people in the United States have hypertension (defined as having a systolic blood pressure [BP] ≥ 140 mm Hg or a diastolic BP ≥ 90 mm Hg, or both) or are taking antihypertensive medications. An additional 6 million people have been told at least twice that they have hypertension. This rising tide is due to an increase in and aging of the population and, more importantly, to an increase in the prevalence of obesity.[1]

No generally accepted definition of hypertension exists. One proposed definition is: *Hypertension is a disorder of intra-arterial pressure regulation such that the longer the duration and the higher the pressure, the greater the risk for target organ damage.* Some definitions include a statement that treatment reduces target organ risk. However it is defined, the reader must recognize that hypertension is heterogeneous in its pathophysiology and that its effect on target organs is also a function of associated risk factors, such as diabetes mellitus, dyslipidemia, and tobacco abuse. The current numeric definitions as promulgated by the Joint National Committee on Prevention, Evaluation, Diagnosis, and Treatment of Hypertension (JNC 7)[2] are displayed in Table 30–1.

The vast majority of patients with hypertension are treated in the ambulatory care setting. Table 30–2 displays general guidelines for follow-up. A few patients need to be treated urgently or emergently on the basis of the clinical presentation of complications of their hypertension rather than on the numbers alone (see Chapter 37). Most adult hypertensive emergencies are associated with very high levels of BP, often in excess of 240/130 mm Hg. What demands emergency treatment, however, is not the number, but an associated condition, such as acute pulmonary edema, acute myocardial infarction, or leaking abdominal aortic aneurysm. A stroke in process should not be treated with aggressive reduction of BP because it may cause brain tissue in the stroke penumbra to become nonviable.[3]

Patients who present repeatedly to Emergency Departments with very high BP but no other symptoms need not be hospitalized or treated emergently. Most of these patients are known hypertensives who have discontinued their medication. Placing them back on their previously prescribed medication is important, as well as adopting strategies to keep them from discontinuing them in the future. Those patients who continue to cycle through emergency departments, especially if they have established target organ damage, are at very high risk for experiencing an acute event.[4] Rapid reduction of BP in such patients with oral nifedipine is definitely contraindicated.

EVALUATION OF THE PATIENT

The subject of this chapter is hypertension, but it is one chapter in a book about cardiovascular therapeutics. One must not lose sight of the global picture of hypertension as part of the constellation of risk factors for cardiovascular, cerebrovascular, and renal disease.

Most medical problems are identified by obtaining a thorough history; performing a detailed physical examination that has, in part, been focused by the results of that history; and then obtaining additional laboratory or imaging data or performing relevant procedures. Hypertension is no exception.

On the other hand, few office-based practices could be self-sustaining if the practitioner asked every question and performed every examination listed in this chapter. The solution lies in a thorough approach that uses the patient and office staff to gather most of the data so that the practitioner

Table 30–1 Classification of Blood Pressure for Adults

BP Classification	SBP (mm Hg)	DBP (mm Hg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥160	or ≥100

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.
From Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.

Table 30–2 Recommendations for Follow-up Based on Initial Blood Pressure Measurements for Adults Without Acute End-Organ Damage

Initial Blood Pressure (mm Hg)*	Recommended Follow-up†
Normal	Recheck in 2 yr
Prehypertension	Recheck in 1 yr‡
Stage 1 hypertension	Confirm within 2 mo‡
Stage 2 hypertension	Evaluate or refer to a source of care within 1 mo
Higher BP (>180/110 mm Hg)	Evaluate and treat immediately or within 1 wk depending on clinical situation and complications

*If systolic and diastolic categories are different, follow recommendations for shorter follow-up (e.g., 160/86 mm Hg should be evaluated or referred to source of care within 1 mo).
†Modify the scheduling of follow-up according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.
‡Provide advice about lifestyle modifications.
From Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.

can convert this to information in short order and take the appropriate next steps. We address these issues as follows.

TAKING THE HISTORY

The history should provide clues as to whether the patient truly has hypertension; whether it is primary or secondary (Table 30–3); and, if secondary, the most likely cause or causes. The relevant questions should be incorporated in a history form that is to be completed by the patient or a knowledgeable family member before coming to the office. Many of the items are common to the history required for other disease entities covered in this book. Some practices may have electronic medical records or other computer capabilities so that patients may enter data at home and transmit them to the office. Use computer programs that require a positive or negative entry rather than defaulting to "negative" or "normal" when no entry is made. Figure 30–1 displays the pertinent elements of the history.

Table 30–3 Selected Causes of Secondary Hypertension

Chronic kidney disease
Coarctation of the aorta
Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy
Drug induced or drug related (includes nonsteroidal anti-inflammatory drugs, illicit pressor agents such as cocaine, sympathomimetics such as nasal decongestants and diet drugs, cyclosporine and tacrolimus, erythropoietin, licorice, alternative agents such as ephedra, ma haung and bitter orange)
Pheochromocytoma
Primary aldosteronism and other mineralocorticoid excess states
Renovascular hypertension
Sleep apnea
Thyroid/parathyroid disease

From Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.

Details of the Present Illness

Determining when the patient first became aware of having hypertension is important. Sudden or very recent onset or exacerbation may increase the likelihood of secondary hypertension. Ask about military, employment, insurance, and other past physical examinations. Determine what readings were obtained by other physicians, such as a gynecologist, or for a procedure like colonoscopy, or perioperatively. Someone who reports decades of being asked to rest before the BP determination is repeated or told that his or her BP is "borderline" (a meaningless term) is less likely to have a secondary cause.

Obtain a history of previous hypertension work-up with particular attention to data that may have already been reliably collected and need not be duplicated. If the patient has been previously treated for hypertension, a detailed list of medications used, their effect (or lack of same), and any adverse effects will be useful. Special attention must be paid to patients who report multiple, pharmacologically improbable and often bizarre "allergies" to medications. This may be a clue to anxiety syndromes or panic attacks. Some of these patients do not have hypertension at all. Furthermore, anxiety-induced hypertension generally does not respond to antihypertensive therapy. These patients require anxiolytic agents and care from a specialist in treating anxiety disorders.

Family History

Family history should be extended when possible to both maternal and paternal grandparents, aunts, and uncles in addition to siblings and children. If a woman has children, inquire about her BP during her pregnancy. Seek information

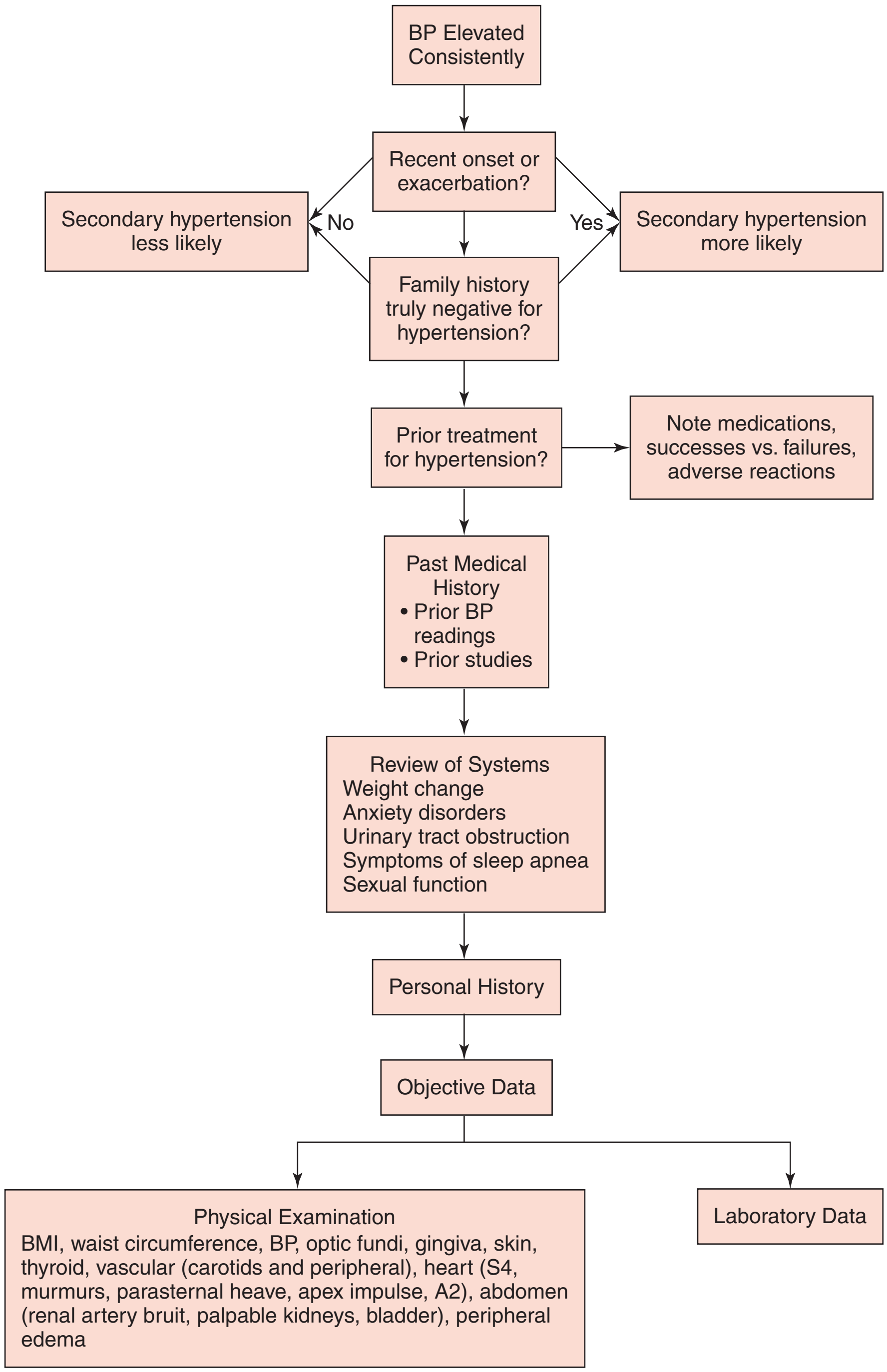

Figure 30–1 Flowchart for initial work-up of hypertension. A2, aortic component of second heart sound; BP, blood pressure; S4, fourth heart sound.

on strokes, premature cardiac death, and kidney failure in addition to heart failure and hypertension.

Past Medical History

Past medical history can reveal opportunities to review medical records for BP readings taken at the time of hospitalizations or procedures or for imaging studies, such as those of the brain or kidneys or laboratory data that may reveal a pattern of, for example, decreased serum potassium levels. A CT or MRI taken because of headaches might prove helpful by being totally normal or by showing signs of hypertension-associated brain lesions.

Review of Systems

The review of systems should focus on recent weight changes and on clues to anxiety disorders. Recent weight gain may be associated with new onset of hypertension. If the patient can lose the weight, it offers the opportunity to normalize the BP without medication. Weight loss may be a clue to hyperthyroidism or pheochromocytoma. Has the patient been previously diagnosed with panic attacks? Has the patient received formal psychological or psychiatric care? Has he or she taken anxiolytic medications? Both men and women should be asked about symptoms of urinary tract obstruction.

Daytime sleepiness or a history of loud snoring, especially when associated with long periods of apnea, is strongly suggestive of obstructive sleep apnea, a condition known to be associated with hypertension.[5]

Personal History

The personal history is often the key to establishing a diagnosis and in formulating a plan of treatment. Establish dietary intakes of sodium, potassium, and calcium. Tobacco abuse should be detailed because of its vasculotoxic effect. Alcohol abuse is an important factor in hypertension. Caffeine abuse, usually through high intake of coffee, can increase BP. Ask about use or abuse of nasal sprays and cold or allergy remedies, as well as weight loss potions that may have a pressor effect. Licorice abuse is an exceedingly rare cause of hypertension, but it is easily curable. People can be exposed to a variety of pressor agents in so-called health foods or herbal remedies. Determine whether patients are taking nonsteroidal anti-inflammatory drugs. Determine the patient's exercise pattern. If he or she does not exercise at all but has no physical contraindication, a prescription of daily walking is a good start.

A patient's education and occupation can provide important clues to the etiology of hypertension. Although industrial lead exposure is not common today, uncontrollable job-related stress is common.[6] Marital history may also give important clues to a patient's BP.

PHYSICAL EXAMINATION

Basic

The patient's weight and height should be determined. Calculating body mass index (BMI) is simple. Also measure the waist circumference. This simple measurement has significant predictive value for metabolic syndrome and coronary heart disease.[7]

Determination of correct diagnosis and treatment depends on accurate assessment of BP. Flawed decisions may result from inaccurate data. The BP guidelines for measurement of office BP outlined by the JNC 7[2] and the American Heart Association[8] are simple and easy to follow. In brief, the patient should be seated comfortably with feet on the floor and back supported and at rest for at least 10 minutes. The patient should not have consumed tobacco or caffeine in the past 30 minutes. The likelihood that the patient may have used illicit vasoactive drugs should be assessed. The bare arm should be fitted with a cuff of correct size, and the arm supported at heart level. The cuff should be inflated until either the radial or brachial pulse disappears from the palpating fingertip. The pressure should then be reduced by a few mm Hg per second until the first Korotkoff sound is heard.

With few exceptions, disappearance of the sounds marks the diastolic pressure. The initial reading should be repeated in both arms with the patient standing. The reading in each arm should be noted by arm side and position. A between-arm difference of more than 10 mm Hg will be seen in only 9% of the population.[9] These people tend to be hypertensive, older, more obese, and more likely to have decreased vascular compliance. Obstructive lesions are rare and should not be sought unless there are other clinical indications.[9] The systolic BP may be higher in one arm, and the diastolic higher in the other. Note the arm used, and use the one with the higher readings for future determination. This will prevent errors based on using inconsistent readings. Many offices use semi-automated BP equipment. Most of these devices use an oscillometric method of BP determination. If the instrument has been validated and the procedures for patient positioning described earlier have been followed, these devices eliminate observer error and free up staff time. Check *www.dableducational.org* to determine whether the instrument has been validated.

When BP values are reported to you by others, be suspicious of numbers that have terminal zeros for both systolic and diastolic pressures. Assuming that the instrument is calibrated in 2-mm Hg intervals, the odds of having a reading such as 160/100 are 1 in 25. If many similar readings are presented, you can safely assume that they were taken or recorded incorrectly or fabricated.

"White Coat" or Clinic Hypertension

Up to 25% of patients will have higher BP readings in the office than at home. This has been termed "white coat" or "clinic" hypertension. Its true impact on cardiovascular morbidity and mortality remains unknown. These patients should not be considered "normal" because they may have some differences (e.g., higher heart rate, less nocturnal fall in BP) from truly normotensive patients and because they tend to develop fixed hypertension later in life.[10] They should be followed and prescribed adoption and maintenance of a healthy lifestyle. Patients or family members who have been trained to use validated instruments may provide valuable data on home BP readings. If home BP readings are used, the criterion for hypertension is 135/85 rather than 140/90.[11] Be aware of the few patients whose fixation on their BP readings does more harm than good. The use of a 24-hour ambulatory BP recording device may be of value for patients who cannot take reliable home BP readings. Recently, patients have been described who have normal readings in the clinic and high readings at home.[12] In contrast to patients with white coat hypertension, patients with masked hypertension may have an increased risk of cardiovascular morbidity and mortality.

Other Physical Findings

All of the following points are parts of the routine physical examination but require special attention for the patient with hypertension. The patient's gait, posture, ability to stand from a supine or seated position, eye movements, facial expressions, and hearing can exclude gross neurologic abnormalities for patients who have no historical clues to neurologic disease. The patient's affect, goal-directed responses (or not) to questions, and body language can give important clues to anxiety, depression, or hostility.

Examination of the skin for café-au-lait spots, neurofibromatomata, hair pattern changes, factitious lesions, and signs of domestic violence may reveal important clues.

Examination of the optic fundi, although a long-standing tradition, has been challenged as to its usefulness in evaluating the hypertensive patient. Even expert observers have difficulty grading degrees of arteriolar vasospasm.[13] On the other hand,

detection of retinal hemorrhages, exudates, papilledema, marked arteriovenous crossing defects, and markedly increased light reflex should alter one's diagnostic and therapeutic strategy. The eyes and facial features may give clues to hyperthyroidism and hypothyroidism, as well as Cushing's syndrome.

Look for gingival hypertrophy. Many patients who receive treatment with dihydropyridine calcium antagonists develop varying degrees of gingival hypertrophy, and this may become problematic.[14] Establishing the negative before initiating therapy is important.

The carotid arteries should be checked for amplitude of pulse and bruits. History and other clues will dictate the thoroughness of the thyroid examination.

Examination of the heart should focus on rate and rhythm, left parasternal heave, displacement of the apex impulse, accentuation of the aortic component of S_2, auscultation for S_4, and auscultation for murmurs, particularly of mitral incompetence. Looking for signs of heart failure is important.

The abdominal examination should include careful auscultation for a bruit of renal artery origin. With the patient supine, listen in the epigastric area and then work toward both flanks. If a systolic bruit is heard, the sensitivity and specificity for renal artery stenosis are poor; however, if the bruit has both systolic and diastolic components and especially if it can be heard over the costovertebral angles with the patient prone, the specificity is much higher.[15] Palpate for enlarged kidneys indicative of polycystic kidney disease. Palpate for an enlarged urinary bladder. A distended bladder may be an important source of sympathetic discharge. Some or all of the BP elevation may be reduced by relieving urinary outflow obstruction.[16]

If coarctation of the aorta is suspected, BP must be measured in the leg and arm. Decreased leg BP may indicate coarctation or other obstructive vascular disease. The radial and femoral arteries should be palpated simultaneously to determine if there is a pulse delay; this is also suggestive of aortic coarctation. These tests should be routine for children with hypertension.

Peripheral pulses should be checked, and peripheral edema should be assessed. Diabetic patients should have a much more thorough examination of the feet including testing for position and vibratory sense.

BASIC LABORATORY EVALUATION

Absent specific clues to secondary hypertension from the history and physical examination, the basic initial laboratory evaluation should be simple.

Urinalysis is important to assess for intrinsic renal disease, as well as damage to the kidney as a target organ. Testing for microalbuminuria, especially in diabetics, has growing impetus as its predictive value for both renal and cardiovascular disease is revealed and the test becomes more readily available.[17]

Serum urea nitrogen and creatinine, especially with an estimate of glomerular filtration rate (eGFR), are important basic tests. Be aware that the formula used in the Modification of Diet in Renal Disease (MDRD) trial may greatly underestimate GFR in normal people.[18] This formula is used by some clinical laboratories to calculate eGFR. The simple Cockcroft-Gault formula ([140-age in years] $\times$ weight in kg/[serum creatinine in mg/dL $\times$ 72]) remains a useful estimator of GFR. The only laboratory test required by this formula is the serum creatinine.

Serum electrolytes may provide important clues to secondary hypertension or other disease entities. Persistent serum potassium levels below 4.0 mmol/L, but still within the normal range, without use of a diuretic or other reason for potassium loss may suggest hyperaldosteronism. This would be further supported by evidence of metabolic alkalosis.

Elevated serum glucose should lead to further testing given the important interaction between hypertension and diabetes. Although not specifically part of the hypertensive work-up, an assessment of serum lipids should be made because of risk factor clustering.

Uric acid has been considered to be a possible independent cardiovascular risk factor.[19] It should be measured before prescribing a thiazide diuretic.

Assays of plasma renin activity and plasma aldosterone levels are not recommended for the initial evaluation of the hypertensive patient. These assays may play a role in the diagnosis of secondary hypertension, as discussed in later chapters.

A baseline electrocardiogram should be part of the initial evaluation of every hypertensive patient. If there is evidence of left ventricular hypertrophy, this should be confirmed with an echocardiogram. An echocardiogram should not be viewed as a routine initial evaluation.

A chest x-ray should be performed only if specifically indicated. It is not part of the initial evaluation of the hypertensive patient.

OVERVIEW OF TREATMENT OF THE HYPERTENSIVE PATIENT

Once the initial evaluation of the patient has been completed, decisions on the choice of therapy should be made. The JNC 7 algorithm (Fig. 30–2) may be a useful guide for most patients. All patients should have the lifestyle modifications that are discussed in the remainder of this chapter initiated and maintained. For those who require pharmacologic treatment, we recommend first identifying any compelling indications (e.g., heart failure, post-myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, recurrent stroke prevention) because a compelling indication may drive the selection of the antihypertensive medication. If there is no compelling indication, then treatment is based on the stage of hypertension, and this is discussed in following chapters.

If the patient fails to achieve the goal BP despite treatment with full doses of three or more drugs, one of which is a diuretic, he or she is defined as having resistant hypertension. This requires careful assessment and attempt at correction of predisposing factors. The most common cause of resistant hypertension is volume overload. Nonadherence to prescribed regimens or prescription of inadequate doses or inappropriate combinations of medications are also common causes of treatment resistance. Many patients do not take their medications as prescribed or do not take them at all. Assessment and treatment of the patient with resistant hypertension are discussed in Chapter 36.

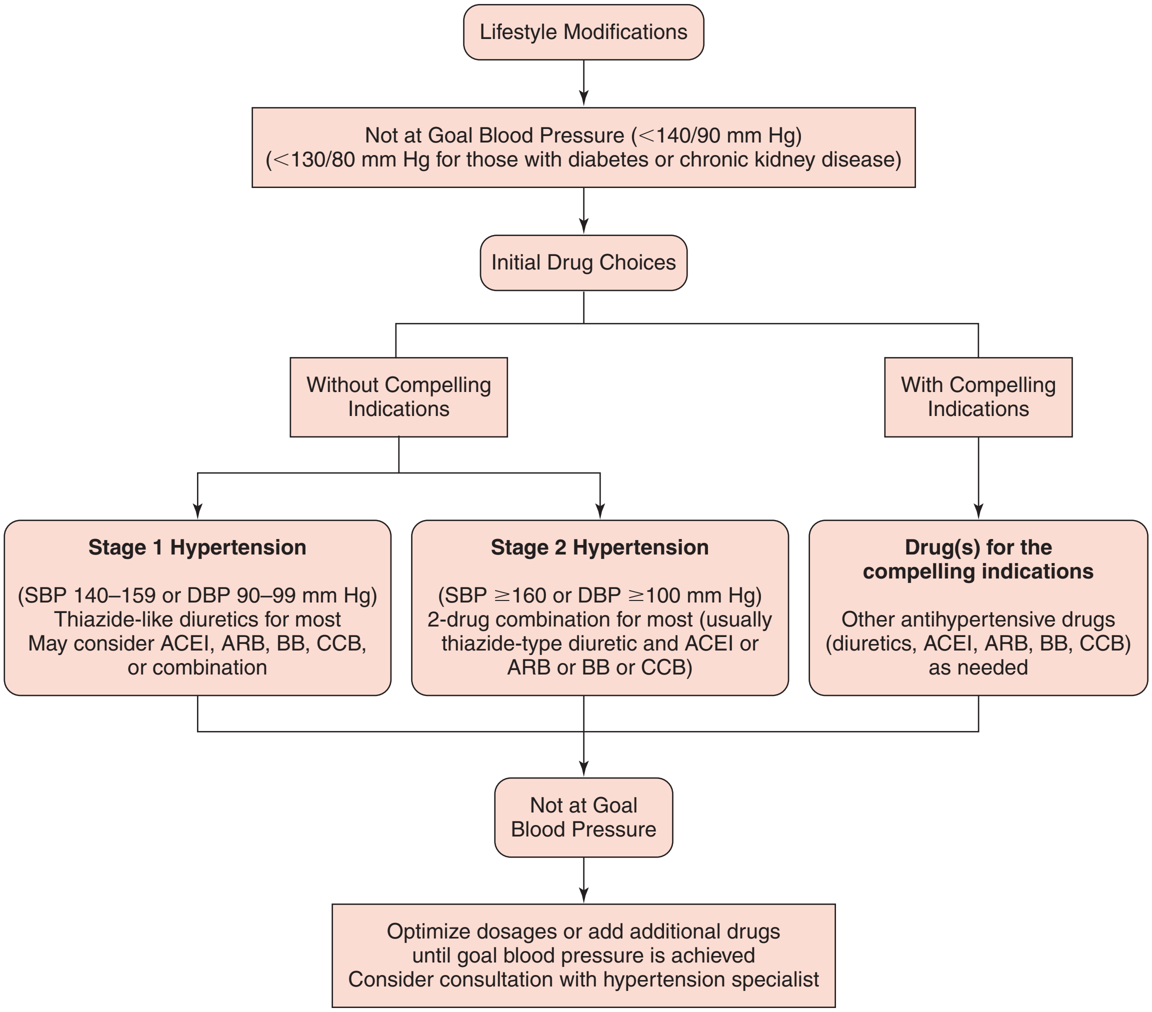

Figure 30–2 Algorithm for the treatment of hypertension. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-adrenergic receptor blocker; CCB, calcium channel blocker. (Modified from Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.)

LIFESTYLE MODIFICATIONS IN THE TREATMENT OF HYPERTENSION

Adopting a healthy lifestyle is a critical component in the prevention and management of hypertension. Despite the availability of effective medical therapy for the treatment of hypertension, BP control rates for patients with this chronic disease are only 31% and far below the Healthy People 2010 goal of 50%.[20,21] In addition to resistance to treatment and poor medication adherence, an unhealthy lifestyle is an important contributor to poor control of BP. Evidence from clinical research studies including randomized controlled trials has demonstrated that lifestyle modification, alone or in combination with antihypertensive medication, decreases BP, enhances the efficacy of antihypertensive medication therapy, and decreases cardiovascular risk.[2] With improved BP control and reduced cardiovascular risk resulting from the adoption of a healthy lifestyle by patients with hypertension, many of the complications associated with hypertension can be prevented (i.e., tertiary prevention[22]).

The major recommendations for lifestyle modifications in JNC 7 include maintaining a normal body weight, consuming a diet rich in fruits, vegetables, and low-fat dairy products, reducing dietary sodium intake, engaging in regular physical activity, and limiting consumption of alcohol (Table 30–4).[2,23-30] Potassium supplementation also lowers BP and should be part of the management plan for prevention and treatment of hypertension.[31-35] An Institute of Medicine report recommended 4.7 g (120 mmol)/day as an adequate intake for potassium in adults.[34] This contrasts with an average intake of approximately 2.0 to 3.0 g potassium/day in most recent surveys in the United States. In the same report an adequate intake for sodium was set at 1.5 g (65 mmol)/day in young adults, 1.3 g/day for those between 56 and 70 years, and 1.2 g/day for those 71 years of age and older. An upper intake level for sodium was set at 2.3 g (100 mmol)/day.[34] The latest statement from the American Heart Association regarding dietary approaches to prevent and treat hypertension endorses these recommendations.[35]

Table 30–4 Lifestyle Modifications for the Management of Hypertension*

Category	Recommendation for Modification	Approximate Systolic Blood Pressure Reduction Range
Weight	Maintain normal body weight (BMI 18.5-24.9 kg/m^2)	5-20 mm Hg/10-kg weight loss[23,24]
Physical activity	Engage in regular aerobic physical activity, such as brisk walking (at least 30 minutes per day, most days of the week)	4-9 mm Hg[28,29]
Diet plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8-14 mm Hg[25,26]
Dietary sodium	Reduce dietary sodium intake to no more than 100 mmol/day (2.4 g sodium or 6 g sodium chloride)	2-8 mm Hg[25,26,27]
Dietary potassium	Increase dietary potassium intake to 120 mmol (4.7 g)	2-7 mm Hg[31]
Alcohol consumption	Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey] in most men and no more than 1 drink per day [0.5 oz of ethanol] in lighter-weight persons and women)	2-4 mm Hg[30]

*The effects of implementing these modifications are dose and time dependent and could be higher for some individuals.
BMI, body mass index.
Modified from Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52, and Appel LJ, Brand MW, Daniels SR, et al: Dietary approaches to prevent and treat hypertension. Hypertension 2006;47:296.

Practical Approaches to Encouraging Lifestyle Modifications

The scientific evidence to date indicates that changes in lifestyle are achievable and sustainable over time provided the approaches are practical, address barriers, and are relevant to the patient. Translating scientific evidence for behavior change into clinical practice presents unique challenges in the management of the patient with hypertension, in part because of the asymptomatic characteristic and chronic nature of the condition. In addition, other factors are associated with adherence to recommendations for the management of hypertension. A conceptual framework presented in Figure 30–3 outlines the link between the risk factors for poor adherence, low adherence to prescribed regimens, poor clinical outcomes, and increased cost and use.[36] Not surprisingly, patients value their quality of life, in general, and how they feel, specifically. Emphasizing improvements in quality of life associated with lifestyle modifications will likely improve adherence to recommendations and ultimately clinical outcomes. Simplifying the complexity of the behavior change and minimizing the side effects of the therapeutic regimen will likely lead to greater adherence. These and the other risk factors listed in Figure 30–3 often present as barriers to following therapeutic recommendations. These system-specific and patient-specific barriers are discussed in subsequent sections of this chapter.

Barriers to Lifestyle Modifications

In order to be effective in encouraging lifestyle modifications, physicians and other health care providers must first understand risk factors for and barriers to following the recommendations. Two broad categories of barriers contribute to poor adherence: system-specific barriers (general access, health care, and environmental barriers) and patient-specific barriers. System-specific barriers include inadequate access to the proper foods and exercise facilities due to high cost, low availability, or lack of transportation to grocery stores and community recreational facilities. Poor access to health care facilities and providers for initial evaluation and ongoing management of hypertension, as well as limited physician and other health care provider knowledge of the lifestyle recommendations including practical approaches to adhering to the recommendations, are other system barriers. Environmental factors, such as climate and unsafe neighborhoods, also contribute to poor adherence.

Patient-specific barriers include limited patient knowledge regarding his or her disease and the importance of lifestyle modifications in the management of high blood pressure and lack of motivation to change behaviors. Other patient-specific barriers are illnesses, such as arthritis or pulmonary disease, which may decrease quality of life, result in significant limitations in the ability to engage in a specific exercise regimen, and increase the complexity of treatment. Sometimes, the patient's cultural and religious background does not support changes in dietary choices and increases in physical activity. These barriers, alone or in combination, may trigger patient use of unconventional or alternative therapies and negatively affect patient adherence to lifestyle modifications. A better understanding of these barriers and their relevance to a particular patient is important in counseling a patient regarding practical approaches to behavior change.

Approaches to Increasing the Adoption of Lifestyle Modifications

In overcoming barriers to lifestyle changes, two general strategies for the management of high BP and its complications are

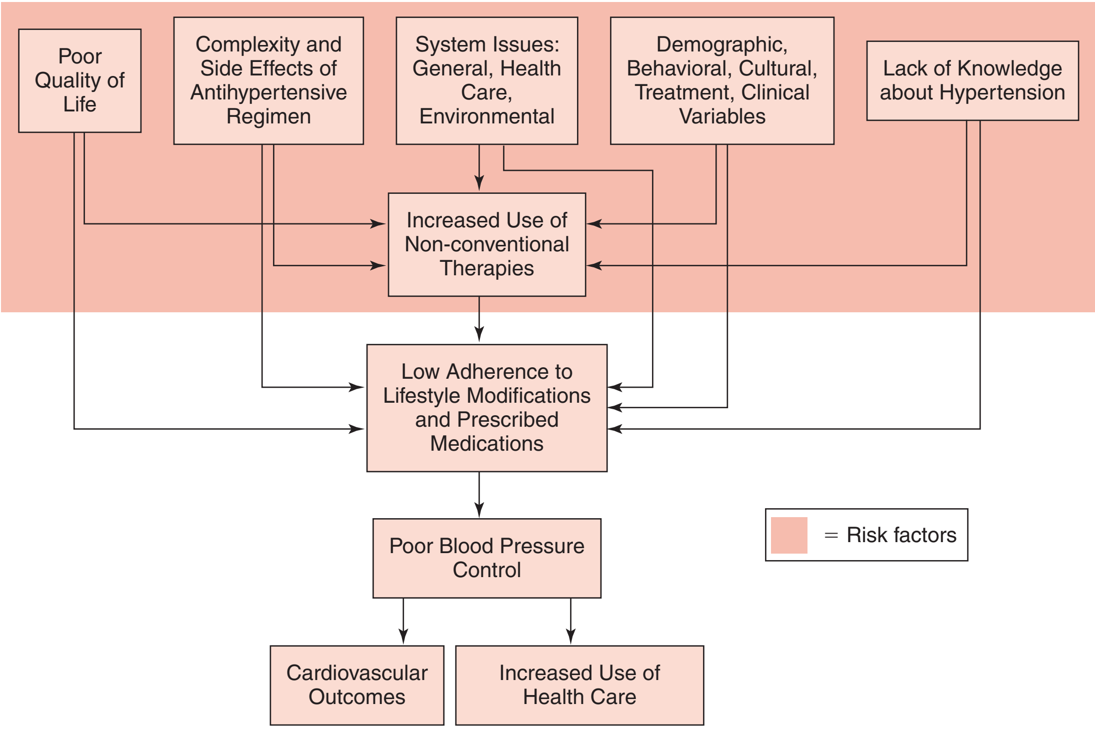

Figure 30–3 Factors associated with patient adherence to antihypertensive therapeutic regimens. (Modified from Krousel-Wood MA, Thomas S, Muntner P, et al: Medication adherence: A key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Curr Opin Cardiol 2004;19:357-62.)

helpful: a system-driven, population-based strategy and a patient-driven, targeted strategy directed at those with overt hypertension. The system-driven, population-based approach strives to achieve a downward shift in the distribution of BP in the general population. Some examples of this approach include providing ready access to healthier lifestyle options for the general population by decreasing sodium content, saturated fat, or caloric density in processed foods, enriching foods with minerals such as potassium, and providing safe and convenient opportunities for exercise in schools and communities.[2,32]

The clinical encounter provides an opportunity to implement the targeted patient-driven approach. In this setting, providers have the chance to explore patient-specific barriers to adherence and tailor recommendations to the individual patient. Advice, per se, is not effective. One key to influencing lifestyle modification is assessing patients' readiness to change and matching the interaction to the patients' readiness to adopt healthy lifestyles.

Readiness for Change

Assessing a patient's readiness for change is based, in part, on stages of change introduced by Prochaska and Velicer.[37] Using these stages, patients are classified as "ready" to follow lifestyle recommendations as follows:

Precontemplation Stage	"I won't"
Contemplation Stage	"I might" in 6 months
Preparation Stage	"I will" in 30 days
Action Stage	"I am" in less than 6 months
Maintenance Stage	"I have" for 6 months or more

Drawing from motivational interviewing strategies,[38] the ALLHAT Dissemination Committee has suggested physicians use the acronym "PICM" in approaching patients regarding lifestyle recommendations: ***Permission***: ask the patient's permission to talk about lifestyle changes; ***Interest***: assess the patient's readiness for change—how interested is the patient in adopting lifestyle modifications on a scale of 1 to 10? (with higher score indicating greater interest); ***Confidence***: ask how sure the patient is that he or she can manage the behavior; ***Match:*** match the health care provider's message to the interest and confidence of the patient.[39] In the clinical setting, if a patient states that his or her interest level in adopting lifestyle changes is a 6, the physician should proceed in eliciting change statements, such as "You are a 6, why are you not a 2 or 3? What would it take for you to be a 7 or 8?" If a patient expresses low interest in changing behaviors, the physician should ask the patient, "Would you be willing to listen to me about why I want you to change?" If the patient expresses low confidence in his or her ability to adopt and maintain change, the physician should ask, "Would you be willing to monitor your activity or diet, think about a plan, and visit with me again about this?" In counseling a patient regarding lifestyle modification, it is important to remember that a patient's readiness for change for one behavior (e.g., reducing caloric intake) may not be the same for another behavior (e.g., increasing physical activity). Differences may also exist, depending on the behavior change desired, in patient readiness to change and interest in communicating with health care providers about the change. In Figure 30–4, readiness for change for physical activity and 3 dietary practices is shown for 59 adult minority patients from 1 of 3 community health centers.[40] In this study, readiness to change and

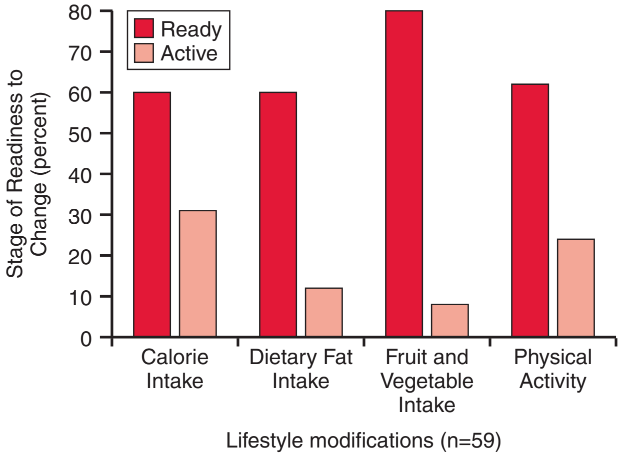

Figure 30–4 Stage of readiness by lifestyle modification. (Modified from Taylor WC, Hepworth JT, Lees E, et al: Readiness to change physical activity and dietary practices and willingness to consult healthcare providers. Health Res Policy Systems 2004;2:2.)

interest in talking to health care providers were separate dimensions. Readiness to change and interest in communicating with health care providers were significantly related for physical activity but not for dietary practices. Patients who were ready for change or actively engaged in physical activity were significantly more interested in discussing physical activity than those classified as not ready to increase physical activity ($P = 0.05$).[40] The goal, nevertheless, is to move patients along a continuum of change; movement toward readiness to change is a key step toward successful adoption of a healthier lifestyle.

Tips for Success in Adopting Healthier Dietary Practices

One way to boost a patient's interest and confidence in adopting healthier dietary practices is to provide simple guidelines for making better choices that can be easily integrated into his or her routine. Understanding the nutritional content of the food he or she eats is an important first step to choosing food that is lower in sodium, fat, and calorie content and higher in minerals, such as potassium and calcium. Reading labels on food products and relating the nutritional content to the lifestyle recommendations before purchasing the products assists adherence. Foods that are lower in sodium and fat are available; however, the patient should realize that the terms *reduced fat* and *fat free* are not synonymous, and neither are the terms *low sodium* and *sodium free* (Tables 30–5 and 30–6). In addition, patients should be aware of the serving size when they are looking for the caloric content of the foods they buy. For example, the calories per serving of most cereals are approximately 110; however, for cereal A the serving size is ¼ cup and for cereal B the serving size is 1 cup. The patient may be surprised that 1 cup of Cereal A for breakfast would result in his or her consuming 440 calories! Choosing snacks like fresh bananas, tomatoes, sweet potatoes, and leafy green vegetables, which are high in potassium, can increase adherence to the potassium supplementation recommendation.

Patients should be encouraged to switch from processed (e.g., canned foods, TV dinners) to unprocessed (e.g., fresh or fresh frozen) foods. Processing of food has a dramatic effect on dietary content of the mineral nutrients. For example, the sodium content of processed canned peas (23.6 mmol/100 g) is much higher than the corresponding content in fresh or fresh-frozen peas (0.1 mmol/100 g). In contrast, the potassium content in fresh or fresh-frozen peas (8.1 mmol/100 g) is much higher than the corresponding content in canned peas (2.5 mmol/100 g). A patient should keep a simple log of the foods and drinks that he or she has consumed over a time period. These logs provide valuable feedback to the patient and provide important information to the health care provider. For example, a patient may bring in a log of foods and drinks consumed over a 2-week period. From review of the information, it may be apparent that the patient drinks six 12-oz soda drinks (not diet drinks) per day. This information might prompt a conversation with the patient regarding the sugar and calorie content of the soda drinks and the benefits of switching to water or other lower-calorie beverages. Some patients may benefit from recording of a more detailed dietary log aimed at identification of the calorie, sodium, and potassium contents of the products.

For patients who are overweight or obese, several recommendations may assist them in their desire to reduce their dietary intake of calories. Patients can limit their consumption of fatty foods by reading labels and choosing fat-free, low-fat, and lower-calorie options. If the patients eat out frequently, modifications in the preparation of foods, such as switching from fried to grilled meats and asking for steamed vegetables in lieu of fried or baked potatoes, can be requested. Food and drinks with a high content of sugar should be avoided. Patients can reduce portion sizes gradually and resist the urge to "supersize" food orders. Fresh fruits and vegetables can be used to replace higher-calorie content snacks, such as chips and cookies. Patients seeking structured diets can adopt meal plans like the DASH diet plan (*http://www.nih.gov/news/pr/apr97/Dash.htm* (accessed September 13, 2006).

Table 30–5 Label Language for Fat

Fat-free	<0.5 g per serving
Low-saturated fat	≤1 g per serving
Low-fat	≤3 g per serving
Reduced-fat	At least 25% less fat than the regular version
Light in fat	One half the fat compared with the regular version

Table 30–6 Label Language for Sodium

Sodium-free	<5 mg per serving
Very-low-sodium	≤35 mg per serving
Low-sodium	≤140 mg per serving
Low-sodium meal	≤140 mg per 3½ oz serving
Light-sodium	At least 50% less sodium per serving than the regular version
Reduced- or less-sodium	At least 25% less sodium per serving than the regular version
Unsalted/no added salt	No salt added during processing

Tips for success in reducing the intake of dietary sodium are also available. Patients should be encouraged to buy fresh or fresh-frozen foods. In addition, patients should read food labels carefully and choose reduced-salt or no-salt-added options. Cured and pickled foods, as well as use of condiments, should be limited. Instead of using salt, patients can season their food with spices. If possible, the patient should avoid or at least limit the use of salt shakers. At restaurants, persons seeking to reduce sodium content should ask for food preparation modifications, such as having the sauce or salad dressing placed on the side of the serving plate.

Tips for Success in Increasing Physical Activity

Engaging in a regular exercise program may be the best way to increase to and maintain physical activity for at least 30 minutes most days (usually 5) of the week. Patients may want to use a home-based exercise videotape regularly for 30 minutes per day on at least 5 days per week, participate in a swimming program for 1½ hours per day on at least 4 days per week at their community recreational facility, plan to walk for 1 hour at least 3 days per week, or play tennis for 2 hours every other day. Patients who choose a plan that has realistic goals, fits into their schedules, and is appropriate for their budgets are more likely to adhere to the program. In addition to enrolling in a formal exercise program, there are many other practical approaches that can be incorporated into a person's daily routine: using the stairs instead of an elevator for going up or down one or two floors, parking further from the entrances of buildings to increase walking, and getting up to change the television channel instead of using the remote control.

General Tips for Adopting Healthier Lifestyles

Other tips for adopting healthier lifestyles include arranging for social support and a periodic review of progress with a knowledgeable counselor. Engaging a family member or friend in the effort to adopt a healthier lifestyle is often of great benefit. Counselors trained in behavior change techniques provide valuable insight into patient-specific strategies for lifestyle modification. As more individuals desire healthy dietary options and practical approaches for increasing physical activity, the demand and ultimately the supply of opportunities for the general population to achieve this goal increase. This creates continuous feedback between system-driven population approaches and patient-driven targeted approaches. Hopefully, as more people adopt healthier lifestyles, the demand and supply of affordable low-fat foods, low-carbohydrate options, and fresh/fresh-frozen fruits and vegetables for the general population will increase.

CONCLUSION

In this chapter we have discussed the initial evaluation and approach to the patient with hypertension. After completing the initial evaluation of the patient, decisions on the choice of therapy should be made. The JNC 7 algorithm may serve as a guide for most patients. For those who require pharmacologic treatment, we recommend first identifying any compelling indications (e.g., heart failure, post–myocardial infarction) that may drive the choice of the antihypertensive medication. If there is no compelling indication, then treatment is based on the stage of hypertension.

All patients should have the lifestyle modifications that are discussed in this chapter initiated and maintained. Lifestyle modifications, such as weight loss, increased physical activity, and dietary changes in individuals, have been shown to improve BP control. Timely adoption of these modifications can reduce complications of this disease and may interrupt the costly cycle of this prevalent chronic disease. As more patients integrate healthier choices into their daily routines, the more likely we will achieve better BP control rates overall, bringing us closer to the Healthy People 2010 goal.

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Pharmacologic Treatment of Hypertension

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CHAPTER CONTENTS

Once the decision is made to begin pharmacologic antihypertensive therapy, several questions arise: Is one drug class more or less appropriate than another in controlling blood pressure (BP) in different types of patients? How long should single-drug therapy continue before a switch to another therapeutic class is made or a second agent is added? Is nonpharmacologic therapy still indicated even when pharmacologic therapy has commenced? Can a patient ever safely discontinue antihypertensive medications and, if so, for how long?

The etiology of long-standing hypertension is generally multifactorial and poorly appreciated in the individual patient. Seldom does one class of drugs succeed in normalizing BP in more than 50% of patients.[1] Furthermore, the initial choice of a medication is often based on nonscientific grounds, anecdotal experience, personal preference, and sometimes intuition. A word-of-mouth approach to therapy sometimes surfaces from successful advertising or promotional efforts, or both, to health care providers and, more recently, patients.

Importantly, a significant proportion of patients who fail to achieve goal BP are suboptimally compliant.[2] Thus the issue of controlling BP is not as simple as choosing the correct first drug or combination of drugs. There is a critical need for a more sophisticated approach to medication-taking behavior on the part of patients with most chronic illnesses. The thoughtful clinician, concerned about optimizing outcomes for patients, brings focus, skills, and perseverance to the challenge of optimizing adherence to a prescription, as well as to the proper diagnosis and evaluation of the hypertensive condition. This chapter addresses many of these issues. Recommendations provided in this chapter should be tailored to a patient's age, gender, race, body habitus, and geographic location.[3]

GENERAL GUIDELINES

Risk Stratification and Treatment

Most current clinical guidelines focus primarily on the management of individual cardiovascular risk factors, such as high BP, hypercholesterolemia, or diabetes. A more appropriate clinical approach to reducing cardiovascular disease (CVD) risk would be based on an all-inclusive assessment of risk profile and accurate stratification of global (absolute) risk in individual patients. Global risk may be logically used as the main determinant of whom to treat, how to treat, and how much to treat. Thus, in some situations, low-risk patients with mildly elevated BP levels would not be recommended for antihypertensive drug treatment, whereas others at high risk but with lower BP would become candidates for treatment.[4] The global risk approach, however, is not consistent with that advanced by the Joint National Committee on Prevention, Evaluation, Diagnosis, and Treatment of Hypertension (JNC-7) and still requires formal testing.[5]

Home Blood Pressure Monitoring

Conventional office BP measurement yields higher BP values than home-based readings, particularly for systolic BP.[6-7] The level of home BP suggested to best correspond to a normal clinic BP of 140/90 mm Hg is approximately 135/85 mm Hg. Home BP monitoring provides a large number of readings and thus adds to the precision of BP determination in a given patient over time.[7-8] Home BP monitoring is useful for the long-term follow-up of patients with white coat hypertension (WCH) and the evaluation of treatment efficacy in patients with sustained hypertension.[7-9] Technical, economic, and behavioral barriers have impeded the widespread use of home monitoring in clinical practice. Two technologic developments, low-cost monitors with memory and systems for telephonic transmission of readings, are likely to overcome these barriers. Such technologic advances are important because many patients will omit or fabricate home readings[10]; thus, devices that have memory or printouts of the readings are recommended.

The number of clinic visits may be reduced with home BP monitoring, making it a potentially cost-effective means for the management of hypertensive patients. Studies have shown that adjustment of antihypertensive treatment based on home BP measurements instead of office BP readings leads to less-intensive drug treatment. Conversely, these studies show that home BP monitoring results in marginally lower costs and poorer BP control, together with no gain in general well-being or left ventricular mass regression.[9] Thus, home BP monitoring requires further validation, and exclusive reliance on self-monitored readings is not broadly recommended.

Comparison among Drugs

Efficacy in Group Trials

The practitioner's selection of a drug to treat hypertension is most often based on the perception of its efficacy in lowering BP and the likelihood of compliance-limiting side effects. In fact, efficacy does not differ meaningfully among the available drug classes.[11-12] Moreover, the recommended starting doses and the sustained release formulations of most drugs preclude BP from being lowered too much or too rapidly, thereby minimizing the risk of hypotension-related side effects. Most oral drugs are designed to lower BP by 10% to 15% in the majority of patients with stage 1 or 2 hypertension and to have similar efficacy. Multidrug comparator trials, such as the Treatment Of Mild Hypertension Study (TOMHS), in which five drugs (chlorthalidone, acebutolol, doxazosin, amlodipine, and enalapril) were compared, showed a BP-lowering response over 4 years that was nearly equal among the drugs tested.[12]

Despite comparable efficacy among classes of antihypertensive agents, individual patient responses may vary considerably, with some of the variability relating to patient-specific determinants, such as race and age. For example, in the Veterans Administration Cooperative Trial, 1292 patients were randomly administered drugs from one of six antihypertensive medication classes (atenolol, captopril, clonidine, diltiazem, prazosin, or hydrochlorothiazide [HCTZ]). The calcium channel blocker (CCB) diltiazem, the angiotensin-converting enzyme (ACE) inhibitor, captopril, and the β-blocker atenolol worked best in blacks, young white males, and older white males, respectively.[11]

The importance of capturing hard endpoint data for individual antihypertensive medications cannot be overemphasized. For example, an analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that despite effective BP reduction by both chlorthalidone and doxazosin, doxazosin use was followed by a two-fold higher CVD event rate, primarily in the form of more frequent episodes of heart failure (HF).[13]

The BP-reducing effect of an antihypertensive medication is important only to the extent that it marks decreases in morbidity and mortality rates. Such hard endpoint data are available for diuretics; ACE inhibitors; CCBs; and, to a lesser degree, β-blockers.[14-15] An overview of placebo-controlled trials of ACE inhibitors showed that with only a modest reduction in BP, these agents decreased the risk of stroke, coronary heart disease, and major CVD events by 20% to 30% among high-risk patients selected on the basis of CVD or diabetes mellitus.[14] A similar overview of placebo-controlled trials with CCBs showed that these agents reduced the risks of stroke and major CVD events by 30% to 40%. It has also been shown that total major CVD events are reduced to a comparable extent in individuals with and without diabetes by regimens based on ACE inhibitors, CCBs, angiotensin receptor blockers (ARBs), and diuretics/β-blockers; thus treatment with any commonly used regimen reduces the risk of total major CVD events, with larger reductions in BP producing larger reductions in risk.[15]

Need for 24-Hour Coverage

The best long-term outcome for hypertensive patients is seen when antihypertensive therapy effectively controls BP throughout a 24-hour cycle of treatment.[16-17] Home BP monitoring rather than office-based readings is necessary to gauge round-the-clock quality of BP control.[16] Drugs that work for 24 hours or longer are particularly attractive choices because they minimize the impact on BP in the 30% of patients who miss a dose of medication at least once weekly.[18] Several long-acting medications, such as the CCB amlodipine, the ACE inhibitor trandolapril, and the ARB candesartan, can maintain continued effect despite a missed medication dose.[19-20]

However, many antihypertensive drugs provide true 24-hour BP coverage only with twice-daily dosing. The failure of a compound to consistently reduce BP over 24 hours can relate to issues of drug half-life, biologic factors dictating whether a patient is a full or partial responder, drug formulation considerations, or a combination of these factors. Importantly, a failure to maintain full effect for 24 hours can be expected to expose the patient to the full brunt of the next day's early morning surge in BP and the attendant risk of an early morning ischemic event.[21]

The medication formulation administered is an important consideration in gaining BP control in the early morning, particularly when nighttime dosing is considered. Nighttime medication dosing should take into consideration two factors: First, does the peak effect of the medication coincide with the natural nocturnal dip in BP, potentially increasing the risk for nocturnal ischemic events?[22-23] Second, is sufficient drug effect still present on awakening to effectively combat the morning surge in BP? Traditional antihypertensive formulations will in most cases cover the morning surge in BP, but only at the expense of an excessive middle-of-the-night drop in BP. This issue can be resolved with new delayed and sustained-release compound technology, which provides peak drug levels to coincide with the morning BP surge, not with the sleep-related fall in BP.[24]

BLOOD PRESSURE GOALS AND THE J-CURVE

Vigorous treatment of BP, down to levels formerly considered harmful, is now suggested, particularly for patients with diabetes or renal disease. This approach has been challenged by studies that concluded that aggressive lowering of diastolic BP can trigger ischemic events rather than provide protection, particularly if critical arterial stenoses are present in the coronary circulation—the "J-curve" hypothesis.[25] Many examples of the J-curve relationship between BP and CVD/non-CVD events reflect reverse causality, where underlying disease (e.g., poor left ventricular function, poor general health, noncompliant arteries) is the basis for both the low BP and the increased risks of both CVD and non-CVD events.[26]

From the Hypertension Optimal Treatment (HOT) study data base, it is reasonable to conclude that for nonischemic hypertensive subjects, lowering diastolic BP to the low 80s mm Hg is both safe and of therapeutic benefit, particularly in diabetic patients. In the HOT study, however, it is unclear whether lowering diastolic BP to below 80 mm Hg was safe or beneficial, or both.[27] In the presence of limited coronary flow reserve, as is seen in coronary artery disease, there is a J-curve relationship between treated diastolic BP and myocardial infarction, but not for stroke.[28-29] Also, a wide pretreatment pulse pressure augurs an increased propensity for CVD

sequelae of hypertension, which can be made more obvious by treatment.[30-31] In such myocardial infarction–prone cases it would be sensible not to bring diastolic BP below the low 80s mm Hg. Practically speaking, if systolic BP is controlled to less than 130 mm Hg, there is marginal benefit, and even the potential for risk, in reducing diastolic BP to less than 80 to 85 mm Hg.

Need to Lower Blood Pressure Gradually

Experts often recommend that BP be brought to goal gradually to avoid sudden and perhaps excessive reductions in cerebral or coronary blood flow. The rate of BP reduction is seldom a problem in the young hypertensive patient, but in the older patient with long-standing hypertension, rapid BP reduction may be poorly tolerated because of diminished cerebral or coronary artery autoregulatory ability.[25,29] If BP drops below the autoregulatory range, symptoms of cerebral hypoperfusion, such as dizziness, fatigue, and forgetfulness, may arise. This is particularly the case in the elderly hypertensive patient, in whom the normal limits of cerebral autoregulation fall around a mean value of 100 to 110 mm Hg. Concern about an "excessive" BP drop in the elderly or the otherwise vulnerable patient should not, however, preclude attempting to reach recommended BP goals within a relatively short time (weeks rather than months) because achieving rapid BP control offers significant benefits to the hypertensive patient who is at high cardiovascular risk.[32]

Choice of Drugs

Many drug options are available for the pharmacologic management of hypertension. The current approach, recommended by JNC 7, suggests that a thiazide-type diuretic be the first medication used in most stage 1 hypertensives but that an ACE inhibitor, an ARB, β-blocker, and CCB are acceptable alternatives.[5] The choice of a starting antihypertensive should be based on the characteristics of the patient—in particular, the presence of concomitant diseases.

The individual characteristics of a patient may influence his or her BP response.[11] An older, overweight black man will likely respond better to diuretic or CCB monotherapy than to a β-blocker or an ACE inhibitor. In general, hypertensive blacks respond better to diuretics or CCBs than to β-blockers, ACE inhibitors, or ARBs. The elderly respond equally well to most drug classes, with the possible exception of β-blockers.[33-35] Women and men respond equally well to most medication classes with the possible exception of CCBs, which produce greater BP reductions in women than men.

The presence of concomitant medical conditions bears on the manner in which hypertension is treated. For example, a hypertensive patient with angina may benefit doubly from either a β-blocker or a CCB. Further, both of these classes may be useful as headache prophylaxis in hypertensive patients with migraines. A logical choice in an elderly male with benign prostatic hyperplasia (BPH) and difficult-to-treat hypertension would be an α-blocker because α-blockers lessen BPH symptomatology and are valuable add-on drugs to multidrug antihypertensive regimens. An ACE inhibitor or ARB would be a suitable choice in a hypertensive patient with heart failure (HF) or proteinuria because these agents reduce the morbidity and mortality rates of HF, as well as urinary protein excretion and the progression of chronic kidney disease (CKD).[36] Conversely, antihypertensive medications may have adverse effects on concomitant conditions (e.g., ACE inhibitors or ARBs in patients with high-grade bilateral renal artery stenosis, high-dose thiazide or loop diuretics in patients with gout).

A stepped-care approach to the treatment of hypertension involves the sequential addition of medications until BP is normalized. The stepped-care approach has heretofore been based mainly on initiating therapy with either a diuretic or a β-blocker. Of late, β-blocker monotherapy has fallen out of favor.[35] ACE inhibitors, ARBs, or CCBs are now viewed as acceptable first-step therapy options. Substitution therapy involves the replacement of one antihypertensive drug class with another and is most appropriate if the drug class first chosen either does not lower BP or is associated with serious or bothersome adverse effects.

A substitution approach to therapy is best applied to stage 1 hypertension because a single drug may often be sufficient for BP control. In stage 2 hypertension, multidrug therapy is more frequently necessary. In this situation, even if the first drug selected is only partially successful in reducing BP, there is no need to substitute another drug. Rather, the stepwise addition of a second or a third medication to the treatment regimen is indicated because the relative ineffectiveness of a first drug can be compensated for by the addition of a suitable second drug. A proper second drug typically is one that has an additive antihypertensive effect to the first drug chosen or reduces the adverse effects of the first drug, or both. To this end, various guidelines—such as JNC 7—now advocate starting two different antihypertensive medications simultaneously if BP is 20/10 mm Hg above goal.[5]

DRUG CLASSES: POSITIONING AND USE

Diuretics: First or Second Line

Thiazide-type diuretics are important primary and adjunctive therapies in the treatment of hypertension. They are useful when administered, even in doses as low as 6.25 mg of HCTZ, in the form of fixed-dose combination therapy.[37] Diuretics are widely promoted for the control of hypertension because they have been shown in numerous controlled clinical trials to decrease hypertension-associated morbidity and mortality rates.[38-39] Diuretics have been recommended as initial treatment in each of the seven reports (1977 to 2003) of the JNC of the National High Blood Pressure Education Program.[5]

The effect of a thiazide diuretic on BP may be divided into three sequential phases: acute, subacute, and chronic, which correspond to periods of 1 to 2 weeks, several weeks, and several months, respectively. In the "acute" response phase, the BP lowering effect of a diuretic is coupled with a reduction in extracellular fluid (ECF) volume and a corresponding fall in cardiac output. The early response (first 2 to 4 days of treatment) to a thiazide-type diuretic, in the setting of a "no-salt-added" diet (100 to 150 mmol/day), results in a net Na^+ loss of 100 to 300 mmol, which translates into a 1 to 2 L decrease in ECF volume, which comes in similar proportions from the intravascular and interstitial compartments. This change in plasma volume can stimulate both the sympathetic nervous and renin-angiotensin-aldosterone (RAA) systems.[40-41]

Later in the course of treatment, thiazide diuretic effects on volume and cardiac output lessen in importance, although BP remains lowered. During the *subacute* phase of the treatment response (first few weeks), plasma volume returns to slightly less than pretreatment levels, despite the continued administration of the diuretic. The *subacute* response phase is a transitional period during which both volume and resistance factors contribute to the BP reduction. The chronic vasodepressor effect of thiazide-type diuretics is more closely related to a persistent reduction in total peripheral resistance than to volume reduction.[42] This process is not so well characterized for loop diuretics. In general, loop diuretics do not reduce BP as well as thiazide-type compounds when given as single-drug therapy, particularly when dosed once a day. Loop diuretics find their greatest use as antihypertensive agents when they can normalize clearly defined, volume-expanded states (Tables 31–1 and 31–2).[43]

The dose-response relationship for BP reduction with a thiazide-type diuretic, such as HCTZ, is flat at doses greater than 25 mg/day.[38,44] Much of the negative biochemical and metabolic experience with diuretics was related to the high doses (100 to 200 mg/day of HCTZ) that were once the therapeutic norm. Metabolically negative side effects, such as hypokalemia, hypomagnesemia, glucose intolerance, and hypercholesterolemia, are uncommon with low-dose diuretic therapy (e.g., 12.5 to 25 mg HCTZ once daily).[39]

The strong evidence that diuretics are effective in preventing target organ damage and CVD outcomes, combined with their excellent tolerability at low doses, supports their use as initial therapy for persons with stage 1 or 2 hypertension and no evidence of target organ damage.[39] Early studies, in which high-dose diuretic therapy was used, showed a lowering of stroke risk but minimal protection from coronary artery disease, perhaps as a consequence of metabolic abnormalities produced by high-dose diuretic therapy. In contrast, low-dose diuretic therapy has been shown to reduce coronary heart disease risk.[45]

In the stage 1 hypertensive, thiazide diuretics lower BP to an extent comparable with most other classes of drugs.[11] Blacks and the elderly typically respond well to diuretics, but not necessarily better than nonblacks or younger patients. Supporting data for the use of diuretic therapy in the elderly are available from the Systolic Hypertension in the Elderly Program (SHEP)[46] and in blacks from the ALLHAT.[47] In SHEP, the diuretic chlorthalidone controlled BP more effectively than did the β-blocker atenolol[46]; likewise, in ALLHAT a chlorthalidone-based treatment regimen effectively controlled BP in hypertensive blacks.[47] Salt-sensitive forms of hypertension, as in the patient with diabetes or renal impairment, or both, may be particularly responsive to diuretic-based regimens. Diuretics are extremely useful adjunctive therapy in situations in which nondiuretic antihypertensive therapy has led to expansion of extracellular volume.

Aldosterone Receptor Antagonists—Second Line

The aldosterone receptor antagonist (ARA) spironolactone contains elements of the progesterone molecule, and its use can be accompanied by progestogenic and antiandrogenic adverse effects, such as painful gynecomastia and other sexual side effects. Eplerenone has a much lower affinity for progesterone and androgen receptors, resulting in a several-fold decrease in progestogenic and antiandrogenic adverse effects.

The onset of action for spironolactone is characteristically slow, with a peak response at 48 hours or more after the first dose. This may relate to a requirement for several days of spironolactone dosing in order for its active metabolites to reach steady-state plasma/tissue levels. Unlike spironolactone, no active metabolites have been identified for eplerenone. The duration of the natriuretic and antikaliuretic effects of spironolactone may differ: The antikaliuretic effect persists for several days after discontinuation of spironolactone, differentiating spironolactone from the shorter-acting ARA eplerenone.[48]

The most extensive antihypertensive treatment experience with ARAs is with spironolactone. Spironolactone has been used with or without a thiazide-type diuretic in the treatment

Table 31–1 Pharmacology of Diuretics

Classes Available
Thiazide diuretics (hydrochlorothiazide)
Thiazide-type (chlorthalidone, indapamide)
Loop diuretics (furosemide, bumetanide, torsemide)
Potassium-sparing diuretics (triamterene, amiloride, spironolactone, eplerenone)

Mode of Action
Early natriuresis and reduction in cardiac output
Long-term decrease in peripheral vascular resistance
Majority of antihypertensive effect at low doses (e.g., ≤25 mg hydrochlorothiazide)
Blockade of aldosterone receptor (spironolactone) and epithelial sodium channel (amiloride and triamterene)

Indications/Considerations in Use
Thiazide-type diuretics are first-line therapy. Loop diuretics are effective antihypertensives when they can specifically correct extracellular fluid volume expansion.
Volume-expanded forms of hypertension not marked by edema.
Salt-sensitive forms of hypertension.
Aldosterone-receptor antagonists are useful in treatment-resistant forms of hypertension.

Contraindications
Prior anaphylactic or Stevens-Johnson–type reactions, or both, to sulfa-type drugs preclude use of sulfa-type diuretics. Less extreme reactions are not an absolute contraindication.

Side Effects
Typically dose dependent
Short-term increase in cholesterol
Increase in new-onset diabetes
Hypokalemia, hypomagnesemia, hyponatremia (mainly with thiazide diuretics)
Hyperkalemia (all potassium-sparing diuretics), gynecomastia (spironolactone)
Hypocalcemia (loop diuretics), hypercalcemia (thiazide diuretics), hyperuricemia
Impotence

Table 31–2 Doses of Diuretics

Drug	Brand Name	Total Dose Range (mg) (frequency/d)	Comment
Chlorthalidone	Hygroton	12.5-50 (1)	More prolonged effect than hydrochlorothiazide.
Hydrochlorothiazide	HydroDIURIL Microzide	12.5-50 (1)	
Indapamide	Lozol	1.25-5.0 (1)	
Metolazone	Mykrox	0.5-1.0 (1)	Improved bioavailability for Mykrox compared with Zaroxolyn; thus the lower dose given. Zaroxolyn remains effective at a GFR < 30 mL/min.
	Zaroxolyn	2.5-10 (1)	
Loop Diuretics			
Bumetanide	Bumex	0.5-4.0 (2-3)	Same as furosemide.
Furosemide	Lasix	40-240 (2-3)	Shorter duration of action; multiple daily dosing to avoid rebound sodium retention. Erratic absorption.
Torsemide	Demadex	5-100 (1-2)	Long duration of action and predictable bioavailability.
Ethacrynic acid	Edecrin	25-100 (2-3)	Only nonsulfonamide diuretic, ototoxicity.
Potassium Sparing			
Amiloride	Midamor	5-10 (1-2)	Hyperkalemia.
Eplerenone	Inspra	50-100 (1-2)	Metabolized by CYP3A4—levels increase with coadministration of verapamil or diltiazem.
Spironolactone	Aldactone	25-100 (1-2)	Dose-dependent gynecomastia, long half-life, hyperkalemia, mg-for-mg more potent than eplerenone.
Triamterene	Dyrenium	25-100 (1-2)	Hyperkalemia.

of essential hypertension and more recently as add-on therapy in the setting of resistant hypertension.[49] Of note, the mg-for-mg BP lowering effect of eplerenone is less than that of spironolactone. The magnitude of the BP reduction with 50-mg of spironolactone twice daily is 1.3 to 2.0 times greater than that seen with eplerenone 50-mg twice daily (or 100-mg once daily).[50]

This add-on effect of spironolactone occurs within weeks, persists for months, and is independent of ethnicity and urinary aldosterone excretion rate. When spironolactone (12.5 to 50 mg/day) was added to a regimen of a diuretic, an ACE inhibitor, or an ARB, a mean decrease in BP of 21 ± 20 mm Hg/10 ± 14 mm Hg and 25 ± 20 mm Hg/12 ± 12 mm Hg was observed at 6 weeks and 6 months of therapy, respectively. The benefit of aldosterone blockade in the general population of patients with resistant hypertension suggests that aldosterone excess may be a more common cause of resistant hypertension than was first believed.[49]

The most common side effect of spironolactone is breast related. Breast symptoms are dose dependent and can include an increase in size (occasionally unilateral); the development of nipple or breast tenderness, or both; the appearance of discrete breast masses; or a combination. Gynecomastia generally corrects on discontinuation of the drug; however, the time required for reversibility can be prolonged, particularly if significant gynecomastia is present. Gynecomastia occurs much less frequently with eplerenone, and eplerenone can be safely substituted for spironolactone in the patient with gynecomastia.[51] Hyperkalemia (>5.5 mEq/L) can occur with ARAs when used in the treatment of resistant hypertension and occurs most typically when ARAs are administered in the setting of either a reduced glomerular filtration rate (GFR) and/or conjoint therapy with an ACE inhibitor or ARB.[48]

β-Blockers: Second or Third Line

The efficacy and side effect profiles of β-blockers are both compound specific and delivery system dependent.[52] β-Blockers have relatively flat dose-response curves for BP reduction and reduce BP without decreasing peripheral vascular resistance.[53] β_1-Cardioselective agents have some advantages, particularly at low doses. One such benefit is a reduced risk of paradoxic pressor effects during major stresses compared with nonselective β-blockade.[54] Nonselective β-blockade may be preferred if certain concomitant illnesses, such as essential tremor or migraine, are present in a hypertensive patient (Tables 31–3 and 31–4).

Over the past decade, national and international guidelines have proposed that β-blockers be used on an equal footing with diuretics for initial therapy of hypertension. This preferred status was based on evidence documenting a reduction in morbidity and mortality rates with β-blocker therapy in hypertension; however, current review of these data find little evidence that β-blocker–based therapy, despite lowering BP, reduces the risk of heart attacks or strokes.[34-35] Moreover, these agents have limited usefulness as monotherapy in a

Table 31–3 Pharmacology of β-Adrenergic-Blocking Drugs

Available Compounds
Noncardioselective (propranolol, nadolol)
Cardioselective (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol)
Intrinsic sympathomimetic activity (acebutolol, pindolol)
Short acting (esmolol)
Combined α- and β-blockers (carvedilol and labetalol)*
Mode of Action
Reduction in cardiac output and heart rate
Little to no change in peripheral vascular resistance
Inhibition of renin release
Direct central nervous system effect
Alteration in catecholamine release or response
Indications/Considerations in Use
Pulse rate-dependent forms of hypertension
Hypertensive persons with symptomatic coronary artery disease
Second-line therapy in congestive heart failure
Essential tremor and headache prophylaxis
Contraindications
Bronchospastic pulmonary disease
Decompensated congestive heart failure
Heart block, sick sinus syndrome
Insulin-dependent diabetes mellitus—cautious use
Side Effects
Bronchospasm
Heart block
Worsening of congestive heart failure
Increased triglyceride and/or decreased high-density lipoprotein levels
Masking of most hypoglycemic symptoms in diabetes mellitus
Depression or nightmares, or both

*Combined α- and β-blockers are also discussed in Table 31–13.

number of patient subsets that include blacks, the elderly, and diabetic patients. Hence, β-blockers should no longer be considered as suitable first-step therapy in the treatment of hypertension.[34-35]

β-Blocker use should be reserved for select circumstances.[55-56] First-step β-blocker therapy is particularly useful for patients with a hyperkinetic form of hypertension, as in individuals with a high cardiac awareness profile or somatic manifestations of anxiety, such as tremor, sweating, and tachycardia.[38] β-Blockers are useful as add-on therapy in hypertensive subjects with tachycardic responses to drugs, such as dihydropyridine CCBs, or vasodilators, such as hydralazine or minoxidil.[57] β-Blockers also have important roles in the treatment of angina pectoris,[58-59] HF with systolic dysfunction,[60] the post–myocardial infarction patient,[61] and diastolic dysfunction (see Chapter 34). When used for secondary prevention in patients after an acute myocardial infarction, the greatest protection has been observed with cardioselective, lipid-soluble agents without intrinsic sympathomimetic activity (ISA). Perioperative hypertension also may be treated with β-blocker therapy.[62]

β-Blocker use for hypertension has been on the decline over the past several years due to the perception that β-blockers are associated with frequent adverse effects. However, these adverse effects are not nearly as troubling as once was believed, particularly if doses are kept within reasonable boundaries. Escalating doses of β-blockers can induce salt and water retention, making diuretics a needed adjunctive form of therapy.[37] Abrupt discontinuation of a β-blocker, particularly when administered in high doses, may be followed by adrenergically mediated withdrawal symptoms.[63] Therefore a stepwise reduction in dose is advised. β-Blockers administered with either verapamil or diltiazem can cause sharp reductions in heart rate; this combination should be used with caution.

Angiotensin-Converting Enzyme Inhibitors: First or Second Line

ACE inhibitors are considered a suitable first-step option in the treatment of hypertension in a diversity of patient types. Enthusiasm for the use of ACE inhibitors extends beyond their effects on BP because they are at best comparable with other drug classes including diuretics, β-blockers, and CCBs for both BP control and most outcome benefits in both diabetic and nondiabetic hypertensives. Response rates with ACE inhibitors range from 40% to 70% in stage 1 or 2 hypertension, with level of sodium intake and ethnicity influencing the overall effect. In the interpretation of clinical trial results with ACE inhibitors, a distinction should be made between the mean reduction in BP (which is typically significant) and the percentage of individuals who are poor, average, or excellent responders (which may vary considerably among studies).[36,64]

The BP-lowering response to ACE inhibition is inconsistently predicted by such markers as ACE gene polymorphism and pretreatment or post-treatment plasma renin activity (PRA) (used as markers of renin-angiotensin axis [RAA] activity), or both. However, when hypertension is marked by significant RAA activation, as in renal artery stenosis, the initial BP response to an ACE inhibitor can be large.[36,64]

ACE inhibitors are generally ineffective as monotherapy in salt-sensitive, low-renin forms of hypertension (e.g., black and diabetic hypertensive persons) unless administered in higher-than-usual doses.[65] However, BP responses to ACE inhibition are so variable that some individuals in these groups experience significant reductions in BP with ACE inhibitor treatment. Further, even those who do not manifest robust BP responses to ACE inhibitors should not be denied the "beyond BP" benefits of this drug class.[66] The low-renin state, characteristic of the elderly hypertensive, differs from other low-renin forms of hypertension in that it reflects senescence-related changes in the RAA axis and not volume expansion. The elderly generally respond well to ACE inhibitors at usual doses,[67] although senescence-related renal failure, which reduces the elimination of most ACE inhibitors, complicates analysis of dose-specific treatment results.[68]

ACE inhibitors show a steep dose-response curve for BP reduction at low doses; thereafter, the dose-response relationship typically flattens. ACE inhibitor use is not accompanied by salt and water retention or increased heart rate. Multiple-dose titrations of an ACE inhibitor are seldom warranted except in HF. In salt-sensitive forms of hypertension, the

Table 31–4 Doses of β-Adrenergic-Blocking Drugs

Drug	Brand Name	Total Dose Range (mg) (frequency/d)	Comment	Fixed-Dose Combination
Acebutolol	Sectral	200-800 (1)	Cardioselective, intrinsic sympathomimetic activity	
Atenolol	Tenormin	25-100 (1)	Cardioselective	Tenoretic
Betaxolol	Kerlone	10-20 (1)	Cardioselective	
Bisoprolol	Zebeta	2.5-20 (1)	Cardioselective, indicated as first-step therapy as combination product	Ziac
Carteolol	Cartrol	2.5-10 (1)		
Carvedilol	Coreg	3.125-25 (1-2)	Combined α- and β-blocker, postural hypotension	
Esmolol	Brevibloc		Short-acting IV form	
Labetalol	Normodyne Trandate	100-400 (2)	Combined α- and β-blocker	
Metoprolol	Lopressor Toprol XL	25-200 (1, 2)	Cardioselective, long-acting preparation available	
Nadolol	Corgard	40-320 (1)		Corzide
Penbutolol	Levatol	10-20 (1)		
Pindolol	Visken	5-15 (2)	Intrinsic sympathomimetic activity	
Propranolol	Inderal Inderal-LA	10-240 (1-2)	Long-acting preparation available	Inderide
Timolol	Blocadren	20-60 (2)		Timolide

addition of a diuretic either as sequential therapy or in the form of fixed-dose combination therapy increases the effectiveness of ACE inhibitors (Tables 31–5 and 31–6).[37]

Results from head-to-head comparison trials support the comparable antihypertensive efficacy and tolerability of the various ACE inhibitors at equivalent doses. However, there are differences among the ACE inhibitors, in time to onset and duration of effect, which may relate to their absorption and tissue distribution characteristics.[36,64] Multiple options exist for orally available ACE inhibitors, but enalaprilat is the lone ACE inhibitor available in an IV form.

ACE inhibitors labeled as “once daily” differ in their capacity to decrease BP for a full 24 hours, as defined by a trough-to-peak ratio >50%, with many patients requiring a second daily ACE inhibitor dose to maintain effect.[19,69] Consequently, the dosing frequency for an ACE inhibitor should take into consideration the highly individualized response patterns to these drugs. Also, ACE inhibitor responses are linked to a patient’s volume state. Thus when intentional volume losses occur (diuretic therapy) or unintended changes in volume occur (sweating/exercise), or both, major decreases in BP can arise.

The rationale for combining a diuretic with an ACE inhibitor is that diuretic-induced sodium depletion activates the RAA system and moves BP to an angiotensin II–dependent mode.[37] Even minimally natriuretic doses (12.5 mg/day) of thiazide-type diuretics reduce BP when given with an ACE inhibitor.[37] A β-blocker can also be given together with an ACE inhibitor, although the incremental effect on BP lowering is minor. β-blockade in this combination blunts the reactive rise in PRA that follows from ACE inhibition. Adding a peripheral α-antagonist, such as doxazosin, to an ACE inhibitor can further reduce BP, albeit with an uncertain mechanistic basis. The BP-lowering effect of an ACE inhibitor is also significantly enhanced with the addition of either a dihydropyridine or a non-dihydropyridine-type CCB.[64,69-70]

ACE inhibitors confer significant benefit to the morbidity and mortality rates in randomized controlled clinical trials in patients with HF[60,71] or progressive renal disease.[72] Thus ACE inhibitors are preferred in the treatment of concomitant illnesses, such as HF, left ventricular hypertrophy (LVH), proteinuric renal failure, and myocardial infarction associated with systolic dysfunction.[60,72,73] ACE inhibitors can restore endothelial function in the patient with endothelial dysfunction and can remodel blood vessels and, in the process, improve vascular compliance.[74] The BP-lowering effect or tissue protection afforded by ACE inhibitor therapy, or both, may be attenuated by the coadministration of aspirin, although the degree of this interaction remains a controversial issue.[75]

Side effects associated with ACE inhibitors include cough, angioedema, and a distinctive form of functional renal insufficiency.[76] Once cough or angioedema has occurred with an ACE inhibitor, there is no advantage to switching to an alternative ACE inhibitor because these are *class effect* phenomena.[77,78] The occurrence of functional renal insufficiency with an ACE inhibitor does not preclude a patient from future ACE inhibitor therapy unless high-grade bilateral renal artery stenosis is present. Although initiation of ACE inhibitor therapy often reduces GFR, these drugs are not intrinsically nephrotoxic (see Chapter 35). No specific level of renal function precludes their use unless clinically relevant hyperkalemia occurs.[79]

Angiotensin Receptor Blockers: First or Second Line

ARBs are suitable first-step options in a diversity of hypertensive phenotypes. As with ACE inhibitors, enthusiasm for the use of ARBs goes beyond their effects on BP because drugs in this class are at best comparable with diuretics, β-blockers,

Table 31–5 Pharmacology of Angiotensin-Converting Enzyme Inhibitors

Available Compounds
Sulfhydryl containing (captopril), phosphinyl containing (fosinopril), and carboxyl containing (all others)
Renally and nonrenally cleared (fosinopril, trandolapril); highly tissue bound (perindopril, quinapril, ramipril, trandolapril)
IV form (enalaprilat)
Information to support the concept of a "preferred" ACE inhibitor based on tissue binding characteristics is inadequate

Mode of Action
Indirect arterial vasodilation by decreasing angiotensin II–related vasoconstriction or vasodilation secondary to an increase in bradykinin, or both
Decreased sympathetic nervous system activity and variably lowered aldosterone concentrations
Decrease in vasoconstrictor substances, such as endothelin or improvement in endothelial dysfunction, or both
Increase in concentrations of the vasodilator peptide angiotensin (1-7)
Absence of a compensatory tachycardia or antinatriuresis with BP reduction

Indications/Considerations in Use
Initial monotherapy of patients with a variety of comorbid conditions accompanying hypertension, such as heart failure or diabetic nephropathy
Enhanced response with addition of a diuretic or a calcium channel blocker
Hypertensive blacks as a group, but not necessarily on an individual patient basis, respond less well
Patients requiring multidrug therapy with otherwise resistant hypertension, such as a diabetic patient or patient with renal failure or unilateral renal artery stenosis
Hypertensive patient with metabolic abnormalities including insulin resistance

Contraindications
Angioedema
Second and third trimesters of pregnancy
Bilateral renal artery stenosis or stenosis in a solitary kidney

Side Effects
First-dose hypotension, particularly if volume contracted
Cough
Angioedema
Functional renal insufficiency—typically requires at least temporary drug stoppage
Small changes in serum creatinine (e.g., a 20% ↑) can occur as a normal response in patients with renal failure; therapy need not be stopped
Increase in serum potassium
Developmental defects in newborns if given in the second or third trimester
Taste disturbances and rash with captopril
Occasional hypoglycemia, particularly with captopril
Anemia secondary to alterations in erythropoietin amount or effect

ACE inhibitors, and calcium channel blockers (CCBs) for BP control and reduction in outcomes. Support for this drug class resides in its ability to prevent new-onset diabetes in at-risk patients[80] and improve renal outcomes beyond what might be expected from BP reduction alone.[81-83] Whether ARB therapy reduces cardiac outcomes in high-risk coronary artery disease patients in a "beyond-the-numbers" fashion is unclear.[84-85]

The pharmacology of the various ARBs including their bioavailability, rate of absorption, volume of distribution, and metabolism (CYP450 or not) has been a matter of considerable discussion. However, for the most part, pharmacologic differences between members of this class are of little practical consequence.[86] All ARBs are eliminated through some combination of renal and hepatic clearance. This distinguishes the ARBs from ACE inhibitors, which are predominantly renally cleared.[87] Duration of receptor occupancy, a surrogate for the BP-lowering effect of drugs in this class, is probably only relevant when low-end doses of ARBs are used. At high-end doses, the impact of drug-specific differences in receptor occupancy or elimination half-life, or both, is reduced.[88]

ARBs are pulse-rate neutral and do not promote salt and water retention or sympathetic nervous system activation. They have a steep dose-response curve for BP reduction at low- to mid-range doses; thereafter, the dose-response relationship is shallow, obviating multiple dose-titration steps. Increasing the dose of an ARB typically does not increase its peak effect; rather, it prolongs the response (Tables 31–7 and 31–8).

Current starting doses of many ARBs (as recommended by package inserts) do not sustain maximal blockade of angiotensin-II effect for a 24-hour dose interval. Thus, it is desirable to start ARB therapy at "higher" doses. However, most health care providers prescribe antihypertensive medications including ARBs at low starting doses and frequently fail to uptitrate appropriately. Head-to-head studies comparing different ARBs at these recommended low-end starting doses can be difficult to interpret when full dose-ranging comparisons have not been undertaken and may unfairly favor one drug in the class over another.[89] Little separates one ARB from another with the exception of losartan, which does not reduce BP as effectively as longer-acting ARBs, such as candesartan, but does have a mild uricosuric effect of uncertain clinical significance.[86] The Food and Drug Administration views the difference between the BP-lowering effects of candesartan and losartan (systolic and diastolic BP 2 to 3 mm Hg lower with 32 mg of candesartan versus 100 mg of losartan) as being sufficient to be cited in the package insert for candesartan.[90]

Response rates with ARBs range from approximately 40% to 70% in stage 1 or 2 hypertension, with sodium intake and ethnicity having some bearing on the overall effect. No reliable predictors of the magnitude of BP reduction in response to an ARB are available. Certain patient groups are recognized as being generally more responsive (high-renin and young hypertensives) or less responsive (low-renin, salt-sensitive, volume-expanded individuals, such as the diabetic and the black hypertensive) to ARB monotherapy. However, the BP response to ARB monotherapy can be highly variable in black and diabetic patients, with some individuals in these groups experiencing significant reductions.[66]

Most ARBs are indicated for once-daily dosing but may occasionally lose efficacy at the end of a dose interval, thereby

Table 31–6 ACE Inhibitors: Dosage Strengths and Treatment Guidelines

Drug	Trade Name	Usual Total Dose and/or Range for Hypertension (Frequency/d)	Usual Total Dose and/or Range for Heart Failure (Frequency/d)	Fixed-Dose Combination*
Benazepril	Lotensin	20-40 (1)	Not FDA approved for heart failure	Lotensin HCT Lotrel
Captopril	Capoten	12.5-100 (2-3)	18.75-150 (3)	Capozide **
Enalapril	Vasotec	5-40 (1-2)	5-40 (2)	Vaseretic
Fosinopril	Monopril	10-40 (1)	10-40 (1)	Monopril-HCT
Lisinopril	Prinivil, Zestril	2.5-40 (1)	5-20 (1)	Prinzide, Zestoretic
Moexipril	Univasc	7.5-30 (1)	Not FDA approved for heart failure	Uniretic
Perindopril	Aceon	2-16 (1)	Not FDA approved for heart failure	
Quinapril	Accupril	5-80 (1)	10-40 (1-2)	Accuretic
Ramipril	Altace	2.5-20 (1)	10 (2)	
Trandolapril	Mavik	1-8 (1)	1-4 (1)	Tarka

*These fixed-dose combinations typically contain a thiazide-like diuretic except for Lotrel, which contains the calcium channel blocker amlodipine, and Tarka, which contains the calcium channel blocker verapamil.
**Capozide is indicated for first-step treatment of hypertension.
FDA = Food and Drug Administration.

necessitating twice-daily dosing. The effectiveness of an ARB can be improved with the addition of a diuretic given either as sequential therapy or as fixed-dose combination therapy. On the basis of experience with ACE inhibitors, it can be expected that addition of a β-blocker to an ARB would have a minimal additional effect on BP unless a significant decrease in pulse-rate occurs with the β-blockade. Alternatively, adding a peripheral α-antagonist, a CCB, or an aldosterone receptor antagonist to an ARB (with or without a diuretic) is likely to lead to a significant additional reduction in BP.[89] ACE inhibitors and ARBs can be administered together, although only a modest additional BP reduction can be expected.[91] In the patient with CHF or proteinuria, additional benefits including a reduction in proteinuria and an improvement in CHF symptomatology are derived from such combination therapy.[92-93]

ARBs have been studied in a number of randomized controlled clinical trials in patients with HF and progressive renal disease.[81,92] These trials have documented BP-independent benefits of ARBs for patients with LVH, HF, and proteinuric renal disease. Of note, in these trials, ARBs have been combined with diuretics and most of the patients have been on combination therapy including 2 to 4 antihypertensive agents. Whether ARBs prevent acute vascular events, such as myocardial infarction, is less clear.[94]

Side effects are uncommon with ARBs. Cough does not occur with ARBs, and angioedema is rare.[95] The occurrence of functional renal insufficiency with an ACE inhibitor does not preclude future therapy with an ARB, unless high-grade bilateral renal artery stenosis exists. ARBs may be used safely in patients with CKD. Hyperkalemia appears to be less common with ARBs than with ACE inhibitors in these patients.[96]

Calcium Channel Blockers: First or Second Line

Calcium channel blockers (CCBs) encompass a heterogeneous group of compounds, with distinctive structures and pharmacologic characteristics. CCBs fall into two major classes: dihydropyridines and nondihydropyridines, a subclass that includes verapamil and diltiazem. Dihydropyridine-type CCBs are generally potent vasodilators, which can prompt activation of the sympathetic nervous system. This does not occur with the non-dihydropyridine CCBs verapamil and diltiazem. Second-generation dihydropyridine CCBs, such as amlodipine or felodipine, are vascular selective, with little, if any, effect on cardiac contractility. Diltiazem and verapamil have modest negative inotropic effects and can inhibit atrioventricular nodal function.[97]

The availability of sustained-release delivery systems for CCBs has simplified the use of these drugs, in part because side effects decrease as the intensity of exposure to drug is lessened. For example, short-acting dihydropyridine CCBs reduce BP abruptly, thereby activating the sympathetic nervous system and potentially inciting coronary ischemia. This process does not occur with long-acting dihydropyridine CCBs, which lower BP gradually and smoothly. The long-term impact of low-grade sympathetic nervous system activation, as occurs with dihydropyridine CCBs, seems not to carry a readily identifiable CVD risk.[13,98-99]

CCBs can have a fairly steep dose-response curve for BP reduction. The amount by which BP is reduced with a CCB is a function of the pretherapy BP; thus the higher the BP at the start of therapy, the greater the drop in BP. The BP reduction achieved as a dihydropyridine CCB is titrated upward in dose will be influenced by the degree to which pulse rate is increased. If a CCB is considered for use in a patient with a pulse rate–related form of hypertension, verapamil or diltiazem is preferred. CCBs have a mild natriuretic effect, which may explain why they have more of an effect on BP reduction in patients on a high-sodium diet.[100] CCBs alter the activity of the RAAS axis: they increase plasma renin activity without a commensurate rise in plasma aldosterone so that the ratio of plasma aldosterone to plasma renin activity falls.[100-101] Activation of the RAAS may offset some of the direct BP-lowering effect of CCBs.

All patient groups are to some degree responsive to CCB monotherapy; however, there are no reliable predictors of

Table 31–7 Pharmacology of Angiotensin Receptor Blockers

Available Compounds
Losartan, candesartan, eprosartan, irbesartan, olmesartan, telmisartan, valsartan

Mode of Action
Indirect arterial vasodilation by blockade at the AT_1-receptor
Possible contribution from AT_2-receptor stimulation
Decreased sympathetic nervous system activity and possibly lowered aldosterone concentration
Decrease in vasoconstrictor substances, such as endothelin or improvement in endothelial dysfunction, or both
Absence of a compensatory tachycardia or antinatriuresis with BP reduction

Indications/Considerations in Use
Patients requiring multidrug therapy with otherwise resistant hypertension, such as a diabetic patient or a patient with renal failure
Hypertensive blacks respond less well as a group to monotherapy
Response is improved noticeably by the addition of a diuretic
Hypertensive patient with metabolic abnormalities including insulin resistance or hypercholesterolemia, or both
ACE inhibitor–responsive patients having developed a cough
Add-on therapy to an ACE inhibitor in patients with proteinuria or heart failure

Contraindications
Angioedema
Second and third trimesters of pregnancy
Bilateral renal artery stenosis or stenosis in a solitary kidney
Baseline increased serum creatinine levels are not a contraindication to use

Side Effects
First-dose hypotension, particularly if volume contracted
Angioedema (rarely)
Functional renal insufficiency—typically requires at least temporary drug stoppage
Small changes in serum creatinine (e.g., a 20% ↑) can occur as a normal response in patients with renal failure; therapy need not be stopped
Increase in serum potassium—less so than with an ACE inhibitor
Developmental defects in newborns if given in the second or third trimester
Anemia secondary to alterations in erythropoietin amount or effect (less so than with an ACE inhibitor)

the magnitude of the BP reduction to a CCB. Low-renin, salt-sensitive, volume-expanded diabetic and black hypertensive patients are more often responsive to a CCB than to an ACE inhibitor or a β-blocker. Age is a relative determinant of response to a CCB. Elderly patients are more sensitive to CCBs as a function of age-related alterations in pharmacokinetics (Table 31–9). This may explain, in part, the usefulness of drugs in this class for isolated systolic hypertension. CCBs differ from ACE inhibitors and ARBs in that their BP-lowering effect is not enhanced with sodium restriction. Although gender has not been viewed as an important factor in the response to antihypertensive agents, oral verapamil is not as well cleared in women and plasma concentrations (and effect) are higher than in men at comparable doses.[102]

First-step CCB therapy is of particular use when concomitant conditions, such as coronary artery disease with angina, intermittent claudication, migraine headaches, and Raynaud's phenomenon, are present.[103] In the presence of HF with systolic dysfunction, if a CCB is required, a dihydropyridine CCB is preferred because diltiazem, and more particularly verapamil, have negative inotropic effects.[104] Rate-lowering CCBs, such as verapamil or diltiazem, are preferred if LVH, diastolic dysfunction, or supraventricular tachyarrhythmias are present. Dihydropyridine CCBs should not be used as monotherapy in hypertensive patients with CKD and proteinuria.[105] Verapamil or diltiazem is preferred for the proteinuric CKD patient.[106] The extent to which the detrimental renal effects of dihydropyridine CCBs are reduced when combined with either an ACE inhibitor or an ARB remains to be determined.

CCBs are useful as second-step therapy. Dihydropyridine CCBs can be effectively combined with a β-blocker, an ACE inhibitor, or a peripheral α-antagonist, such as doxazosin or terazosin.[57,70,107-108] Nondihydropyridine CCBs can also be combined with an ACE inhibitor or a peripheral α-antagonist, but their use with a β-blocker is not recommended.[109-110] The combination of a diuretic with a CCB produces an additive response at most. Fixed-dose combination products containing a CCB and an ACE inhibitor are available (e.g., benazepril and amlodipine, felodipine and enalapril, or trandolapril and verapamil) (Table 31–10).[37]

Analysis of data from nine randomized trials comparing different treatment approaches in 62,605 hypertensive patients found that CCBs afforded CV protection compared with that seen with diuretics and β-blockers.[111] In addition, a meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration observed that a CCB-based treatment regimen lowered the rate of stroke by 7% compared with diuretic-β-blocker–based regimens and by 12% compared with ACE inhibitor–based regimens.[14] The positive effect of CCB therapy on reducing stroke occurrence is further supported by the findings of a meta-regression analysis by Verdecchia et al[112]; CCBs, however, have been shown to be less beneficial than diuretics, β-blockers, or ACE inhibitors in prevention of HF.[14]

CCB use can be associated with a variety of troubling side effects, such as polyuria, gastroesophageal reflux, and gingival hyperplasia.[113] Peripheral edema, however, is the side effect that has the greatest impact on the continued use of these drugs. Peripheral edema is due to a disproportionate change in arteriolar resistance, whereby precapillary hydrostatic pressures increase, favoring a fluid shift into the interstitial compartment. CCB-related edema is more common in women and relates to upright posture, age, and choice and dose of the CCB. It can be slow to resolve without intervention.[114]

Strategies for treating CCB-related edema include switching CCB classes; reducing dosage; and adding a venodilator, such as a nitrate, an ACE inhibitor, or an ARB, to the treatment

Table 31–8 Doses of Angiotensin Receptor Blockers

Drug	Brand Name	Total Dose Range (mg) (frequency/d)*	Comment	Fixed-Dose Combination
Candesartan	Atacand	8-32 (1)	Indicated in heart failure	Atacand/HCT
Eprosartan	Teveten	400-800 (1-2)		Teveten-HCT
Irbesartan	Avapro	75-300 (1)	Indicated in type 2 diabetic nephropathy	Avalide
Losartan	Cozaar	25-100 (1-2)	Uricosuric, indicated in type 2 diabetic nephropathy and to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy	Hyzaar
Olmesartan	Benicar	20-40 (1)		Benicar HCT
Telmisartan	Micardis	20-80 (1)		Micardis HCT
Valsartan	Diovan	80-320 (1)	Indicated in heart failure and post-MI	Diovan HCT

*Higher top-end doses are occasionally employed when the full antiproteinuric effect of an ARB is sought.

Table 31–9 Pharmacology of Calcium Channel Blockers

Available Compounds
Phenylalkylamines (verapamil)
Benzothiazepines (diltiazem)
Dihydropyridines (amlodipine, felodipine, isradipine, nifedipine)

Mode of Action
Decrease cellular calcium entry via the L-type channel with a reduction in total peripheral resistance
Negative inotropic and chronotropic effects (nondihydropyridines)
Interference with angiotensin II, α_1, and α_2-adrenergic agonist–mediated vasoconstriction
Natriuresis

Indications/Considerations in Use
Sodium-sensitive and sodium-resistant forms of hypertension
Concomitant diastolic dysfunction (nondihydropyridines) or variant angina
Concurrent cerebral vascular disease
Cyclosporine therapy; verapamil and diltiazem decrease its metabolism and thereby the amount necessary to maintain therapeutic drug levels
Grapefruit juice increases the absolute bioavailability of felodipine, nisoldipine, and nicardipine

Contraindications
Heart block and congestive heart failure (nondihydropyridines); cautious use of verapamil or diltiazem with β-blockers

Side Effects
Tachycardia (dihydropyridines); bradycardia, heart block (nondihydropyridines).
Acute myocardial infarction (short-acting dihydropyridines); heart failure (nondihydropyridines)
Headache, peripheral edema without weight gain (dihydropyridines and nondihydropyridines)
Gingival hyperplasia (dihydropyridines and nondihydropyridines)
Gastroesophageal reflux (dihydropyridines and nondihydropyridines)
Constipation (verapamil)

regimen. ACE inhibitors have been best studied in this regard. Diuretics may reduce the edema somewhat, but at the expense of further reducing plasma volume. Traditional measures, such as limiting the amount of time that a patient is upright and use of graduated compression stockings, are useful adjunctive therapies. When all else fails, CCB therapy can be discontinued and an alternative antihypertensive therapy given.[114]

Most side effects of CCBs are class specific, with the exceptions of constipation and atrioventricular block, which occur more commonly with verapamil. A final consideration relates to drug interactions. The bioavailability of a number of CCBs is increased when they are taken with grapefruit juice.[115] Verapamil and diltiazem can slow the metabolism of cyclosporine. This may prove advantageous from a cost point of view because it may result in the use of lower doses of cyclosporine.[116]

α-Adrenergic-Receptor Blockers: Third Line

α_1-Adrenergic-blocking drugs (α_1-blockers) effectively reduce BP in a manner comparable with other major drug classes. α_1-Blockers have evolved from short-acting compounds, such as prazosin, to longer-acting compounds, such as doxazosin, which has simplified their use (Table 31–11). These compounds are most effective when patients are in the upright position, reducing systolic and diastolic BPs by 8% to 10%.[117]

α_1-Blockers incrementally reduce BP when combined with most drug classes and are the only antihypertensive drug class to improve plasma lipid profiles and reduce insulin resistance.[118-119] In the difficult-to-treat hypertensive, these compounds reduce BP significantly, when used as adjunctive therapy to ACE inhibitors or CCBs. Dose escalation of an α_1-blocker can trigger renal Na^+ retention, and the ensuing volume expansion can attenuate its BP-lowering effect. Thus α_1-blockers should be given with a diuretic unless doses are kept very low.[120-121] First-dose hypotension or syncope is less common with doxazosin or terazosin than with shorter-acting α_1-blockers. However, orthostatic hypotension can occur with these compounds, particularly in volume-contracted patients. Dizziness, headache, and drowsiness are other common side effects of α_1-blockers.[120]

A modest decline in the use of doxazosin and other α_1-adrenergic blocking drugs occurred coincident with the early termination of the doxazosin treatment arm in the

Table 31–10 Doses of Calcium Channel Blockers

Drug	Brand Name	Total Dose Range (mg) (frequency/d)	Comment	Fixed-Dose Combination
Dihydropyridines				
Amlodipine	Norvasc	2.5-10 (1-2)	Very long acting	Amlodipine and benazepril (Lotrel)
Felodipine	Plendil	2.5-20 (1)	Plasma levels increased with grapefruit juice intake	Felodipine and enalapril (Lexxel)
Isradipine	DynaCirc, DynaCirc SR	2.5-5 (1-2)	Dose-dependent increase in heart rate—similar to all drugs in this class	
Nicardipine	Cardene SR	30-60 (2)	Plasma levels increased with grapefruit juice intake	
Nifedipine	Procardia XL, Adalat CC	30-120 (1-2)		
Nimodipine		60 (4-6)	Indicated for subarachnoid bleed	
Nisoldipine	Sular	10-40 (1)		
Nondihydropyridines				
Diltiazem	Cardizem, Cardizem CD or SR, Tiazac	120-360 (1)	Immediate-release form requires multiple daily doses Inhibits cytochrome 3A4	
Verapamil	Calan, Calan SR, Isoptin, Covera-HS,* Verelan PM*	120-360 (1)	Immediate release forms given three times daily	Verapamil and trandolapril (Tarka)

*Nocturnal dosing indicated.

ALLHAT.[13,122] However, α_1-blockers remain important elements of the treatment plan for symptomatic benign prostatic hyperplasia (BPH), typically improving both symptom score and urinary flow in men with BPH. It should not be presumed, however, that patients receiving α-adrenergic blocking drugs for lower urinary tract symptoms are being optimally treated for their hypertension, as has been put forward by the American Urologic Association.[123] Uroselective α-adrenergic blocking drugs have been developed to treat individuals with BPH and for the most part do not lower BP.[124] This highly selective form of BPH therapy typically avoids the vasodepressor risk of α_1-adrenergic blockade in normotensive patients.

Central α-Agonists: Second or Third Line

Central α-agonists have had a lengthy history, starting with α-methyldopa, which has seen its use limited because of bothersome side effects. Clonidine is the most commonly prescribed member of this class (Table 31–12). A small dose of clonidine (0.1 to 0.2 mg twice daily) augments the BP-lowering effect of most other agents and can be reliably used as add-on therapy. Dose titration of clonidine beyond 0.4 mg daily is commonly followed by troubling side effects, such as sluggishness and dry mouth. These side effects can also occur at lower doses (see Table 31–12).[125] Escalating doses of clonidine often bring on salt and water retention; thus, when clonidine or a similar compound is administered, a diuretic becomes useful adjunctive therapy.[126]

Clonidine is available in a transdermal delivery system, which offers distinct therapeutic advantages but is limited in its use by issues of cost and skin irritation (see Table 31–12). Transdermal clonidine is particularly useful in the management of the labile hypertensive patient who requires multiple medications, the hospitalized patient who cannot take medications by mouth, and the patient prone to early morning surges in BP. At equivalent doses, transdermal clonidine is more likely than oral clonidine to precipitate salt and water retention.[127]

Clonidine has become a mainstay of therapy for hypertensive urgencies because of its ease of use and relative safety.[128] Its hourly administration, in doses of 0.1 to 0.2 mg, successfully reduces BP in many patients with hypertensive urgencies. Rebound hypertension occurs in some patients receiving oral clonidine if the drug is suddenly terminated. Particularly vulnerable are patients with excessive adrenergic tone and those receiving high doses of clonidine or concomitant β-blocker therapy that is continued while discontinuing clonidine. Rebound hypertension can be avoided by frequent dosing of oral clonidine (three or four times daily) or by use of a transdermal delivery system. Clonidine overdose produces paradoxical hypertension when the depressor effects of central α_2-adrenergic receptor stimulation are exceeded by the pressor effects of peripheral α_2-adrenergic receptor stimulation, resulting in a predominantly vasoconstrictor response.[129]

Combined α- and β-Adrenergic Receptor Blockers: Second or Third Line

Drugs in this class are nonselective β-blockers without sympathomimetic activity. These compounds reduce peripheral resistance even as their β-blocking effect exceeds their potential

Table 31–11 Pharmacology of α-Adrenergic Receptor Blockers

Available Compounds
Prazosin, terazosin, doxazosin

Mode of Action
Direct arterial vasodilation with minimal effect on the renin-angiotensin-aldosterone axis
Dose-dependent pseudotolerance for BP effect linked to sympathetic nervous system activation or fluid retention, or both

Indications/Considerations in Use
Multidrug requiring patient with otherwise resistant hypertension, such as a diabetic or chronic kidney disease patient
Hypertensive patient with metabolic abnormalities, including insulin resistance and hypercholesterolemia
Hypertensive patients with benign prostatic hyperplasia

Dosing Considerations
Prazosin: Effectiveness relates to the degree of sympathetic activation, which is, in turn, dependent on whether an immediate or sustained-release formulation is being used.
Terazosin: Most BP lowering occurs at the low- to mid-dose range, such as 5-10 mg. Some patients require higher doses. More effective in the upright position.
Doxazosin: Most BP lowering occurs at the low- to mid-dose range, such as 4-8 mg. Some patients require higher doses. More effective in the upright position.

Contraindications
The presence of heart failure dictates careful use

Side Effects
Fluid retention or tachycardia, or both (dose-dependent)
Lethargy, fatigue, dizziness, headache, orthostatic hypotension, first-dose hypotension
Urinary incontinence in women

Table 31–12 Pharmacology of Central α-Agonists

Available Compounds
Alpha-methyldopa, clonidine, guanfacine, guanabenz

Mode of Action
Decreased sympathetic nervous system activity and lowered plasma renin activity by central adrenergic receptor stimulation
Modest reduction in heart rate

Indications/Considerations in Use
Patients requiring multidrug therapy with otherwise resistant hypertension, such as diabetic and renal failure patients.
Primary therapy for patients with sympathetically driven forms of hypertension.
Perioperative forms of hypertension. An anesthesia- and analgesia-sparing property of these drugs may prove beneficial.
Adjunct therapy in systolic forms of heart failure.

Dosing Considerations
Clonidine: Oral clonidine is best given two to three times daily. It is a short-acting compound so that patients with excessive sympathetic activity can have a short-lived response to it. A 1- to 2-day delay in the onset of action after initial patch application with transdermal clonidine exists, making it inappropriate for the management of hypertensive emergencies.
Guanfacine: The initial response to guanfacine is delayed compared with clonidine, but its longer duration of action allows it to be effectively dosed in a range of 1-3 mg given once or twice daily in a split-dose.

Contraindications
None

Side Effects
Fluid retention and bradycardia—dose dependent
Sedation and dry mouth
Skin irritation with transdermal clonidine delivery systems
Autoimmune hemolytic anemia, fever, liver dysfunction (α-methyldopa)
Rebound hypertension with clonidine, particularly if it is stopped and β-blocker therapy is continued or substituted
Large overdoses can paradoxically increase BP

for α-blockade (Table 31–13).[130] Their pharmacodynamic profile is a result of different receptor selectivity of their component stereoisomers, rather than combined α/β-blocking activity in a single chemical entity. Their use has generally been reserved for the complicated hypertensive patient when an antihypertensive effect beyond β-blockade is desired.[131] Sodium retention can occur with higher doses of labetalol.[132] Labetalol, either orally or intravenously, has been used to treat hypertensive emergencies, particularly when associated with cocaine use or in the postoperative setting (see Table 31–13).[133] Carvedilol has been studied more extensively than labetalol from an outcomes perspective. It has been shown to reduce urinary protein excretion more than metoprolol in hypertensive diabetic patients.[134] Carvedilol does not adversely affect glycemic control to the same degree as a traditional β-blocker, such as metoprolol,[134] and is effective in the patient with HF and systolic dysfunction.[135] Carvedilol has added benefit for the HF patient treated with ACE inhibitor or spironolactone therapy.[136]

Direct Vasodilators: Third Line

Hydralazine is seldom used in the management of hypertension, having been supplanted by safer and more convenient and effective agents. Hydralazine must be given in multiple daily doses. The third-line status for hydralazine in hypertension therapy, in part, relates to the lack of outcomes studies to support its use. Its use is generally confined to the setting of

Table 31–13 Pharmacology of Combined α- and β-Adrenergic Blockers

Available Compounds
Labetalol, carvedilol

Mode of Action
Nonselective β-blockers, α-blocking activity
Reduction in total peripheral resistance and heart rate

Indications/Considerations in Use
May be more effective in hypertensive blacks
Patients with chronic kidney disease
Patients with heart failure (caution: large doses can precipitate heart failure)
Hypertensive emergencies
Perioperative management of pheochromocytoma
Patients with aortic dissection
Rebound hypertension with clonidine
Cocaine-related hypertensive crisis

Dosing Considerations
Labetalol: 200-1200 mg/d administered twice daily. Given parenterally as intermittent bolus therapy (10-20 mg IV every 5-10 min) or a continuous infusion (0.5-2.0 mg/min). Dose and dose frequency can be adjusted according to clinical circumstances.
Carvedilol: 12.5-25 mg twice daily for hypertension; 25-50 mg twice daily for angina

Contraindications
Same as with β-blockers
Cautious use in patients with liver disease

Side Effects
Bronchospasm
Heart block
Heart failure
Transaminase elevation (labetalol)
Postural hypotension, fatigue, gastrointestinal symptoms, scalp tingling

pregnancy-induced hypertension and HF in the patient who is intolerant of ACE inhibitors.[137-138]

Minoxidil is a potent vasodilator that is generally reserved for refractory hypertensive patients. Early use of minoxidil can simplify the process of establishing BP control in the hypertensive patient, requiring several antihypertensive medications for BP control. Minoxidil is generally given together with a diuretic and a β-blocker to combat its tachycardic and salt-and-water retaining effects. These counter-regulatory responses can effectively negate its BP-lowering effect.[139] Hypertrichosis is common with minoxidil and can be disfiguring, particularly in women. Hair growth begins within 3 to 6 weeks of starting therapy, occurring over the temples and eyebrows initially, spreading to areas between the eyebrows and hairline or sideburn regions, to finally involve the trunk, extremities, and scalp. Hypertrichosis usually disappears within a few weeks of discontinuing minoxidil, though in some cases the process is prolonged (Table 31–14).

Table 31–14 Pharmacology of Direct Vasodilators

Available Compounds
Hydralazine, minoxidil

Mode of Action
Direct arterial vasodilation with minimal venodilation
Reflex activation of sympathetic nervous and renin-angiotensin-aldosterone systems

Indications/Considerations in Use
Patients requiring multidrug therapy with resistant hypertension and refractory to other agents, particularly patients with chronic kidney disease
Minoxidil loading over 24-36 hr can quickly establish BP control in hypertensive emergencies

Dosing Considerations
Hydralazine: Total dose of 75-300 mg given two to four times daily. The incidence of systemic lupus erythematosus is higher in patients receiving large doses.
Minoxidil: Total dose of 2.5-40 mg given once to three times daily. Usually requires coadministration of a diuretic (loop diuretic and metolazone combination may be warranted), a β-blocker, and an ACE inhibitor. The LVH seen with minoxidil is best treated with an ACE inhibitor.

Contraindications
Pericardial effusion (minoxidil)
Dissecting aortic aneurysm

Side Effects
Fluid retention
Tachycardia
Lupus-like syndrome (hydralazine)
Pericardial effusion (minoxidil)
Hypertrichosis (minoxidil)

SPECIAL CONSIDERATIONS

Women

Hypertensive complications are less common in women than men, except in the older age groups. Early trial results suggested greater efficacy of antihypertensive drug treatment in the prevention of CVD-related complications and death in men than in women; however, more recent trials, such as ALLHAT, which included 19,865 women among its 42,448 high-risk hypertensive participants, showed no gender difference between treatments (amlodipine/chlorthalidone and lisinopril/chlorthalidone) in the primary coronary outcome measure or in all-cause mortality.[140]

Women respond to most therapies similarly to men and the thresholds and goals of antihypertensive therapy, and choices of antihypertensive drugs are generally the same for both genders.[141-142] Of note, data collected in the Women's Health Initiative Observational Study indicate an increased CVD risk for women being treated with CCBs as monotherapy

or in combination with diuretics.[143] However, as in all observational studies, there is uncertainty as to the ability to control fully for confounding by indication.[143] Moreover, these findings differ from those in a large meta-analysis of randomized controlled trials,[14] as well as in important individual clinical trials,[144-145] which demonstrated no differences between the effects of regimens based on CCBs, ACE inhibitors, ARBs, or diuretics/β-blockers on CVD mortality.[15]

Some special considerations may influence treatment choices in women. Thiazide-type diuretics are useful in women, particularly in older women, in that they decrease urinary calcium excretion and thus decrease fracture rate.[146] β-Blockers tend to be less effective than in men. Women more commonly experience side effects with all antihypertensive medications and are more liable to certain compound-specific side effects[147] (e.g., diuretic-induced hyponatremia,[148] ACE inhibitor-related cough,[149] CCB-induced vasodilatory edema,[150] and minoxidil-induced hirsutism).[139] Further, ACE inhibitors and ARBs should be used cautiously in women planning to become pregnant because of the high risk of serious fetal developmental defects if exposed to these medications during the second and third trimester.

Blacks and Other Ethnic Groups

Blacks have a higher prevalence of hypertension and more significant target-organ disease including end-stage renal disease, LVH, and nonischemic HF.[152-155] Intrauterine growth retardation and excessive early childhood weight gain appear to forecast future hypertension and possibly the development of CKD in blacks.[156] The distinct pathophysiology of hypertension in blacks may affect the response to antihypertensive therapy (Tables 31–15 and 31–16). In particular, aldosterone-induced volume expansion and a nondipping nocturnal BP pattern are increasingly recognized as important contributors to the progression of hypertension and related target organ damage in blacks.[157-158]

The treatment of hypertension in blacks is complex, with socioeconomic and behavioral issues, as well as health care beliefs, typically influencing the success or failure of a particular regimen.[159] When these factors are coupled with the high rates of obesity and smoking in blacks, the treatment of hypertension becomes exceedingly complicated.[160-161] Given equal access to health care resources, however, blacks often respond to antihypertensive treatment comparably with whites.[160] Moreover, the majority of whites and blacks have similar responses to most commonly used antihypertensive drugs (Fig. 31–1). Therefore, clinical decisions to use a specific drug should be made on an individualized and not a group basis.[66]

Despite the overall similarity of responses to antihypertensive treatment in blacks and whites, there are some differences

Table 31–15 Special Considerations Relative to Target Organ Disease in Hypertensive Blacks

- Cerebrovascular accidents and, in particular, intracerebral hemorrhage are more common in blacks than in whites.
- The incidence of end-stage renal disease is several-fold higher in blacks than in whites and the profibrotic growth factor transforming growth factor-β_1 (TGF-β_1) is hyperexpressed in black patients with hypertension and those undergoing hemodialysis.
- LVH is more prevalent in blacks than in whites, which may in part explain the higher rate of sudden cardiac death in blacks. Exercise favorably affects LVH in hypertensive blacks.
- There is a disproportionate rate of coronary heart disease deaths in blacks, particularly in black women, compared with whites, possibly related to a greater clustering of known coronary artery disease risk factors.
- Hypertension is a major predisposing factor for the development of heart failure in black patients.
- Obesity, particularly in black women, may contribute to the high rates of hypertension and target organ injury in blacks.
- Nocturnal “nondipping” BP patterns and nighttime BP elevations are more common in blacks than in whites.
- Endothelin levels are generally increased and nitric oxide bioavailability reduced in hypertensive blacks compared with hypertensive whites.

LVH, left ventricular hypertrophy.

Table 31–16 Treatment Considerations in Hypertensive Blacks

- Hypertension is more common and more severe in blacks than in whites, and there is a persistent high rate of undetected, untreated, and uncontrolled hypertension in blacks.
- Target organ damage is more likely to present in blacks for any given level of BP.
- Intrauterine growth retardation in black infants, as well as excessive weight gain in adolescence, are determinants of high BP.
- The hypertensive black is likely to be younger than his or her white counterpart, therefore presenting potential age-related problems with medication compliance.
- Response to a variety of drugs or combinations of drugs may be different from other racial/ethnic groups. Blacks have a higher incidence of cough and angioedema with an ACE inhibitor.
- Socioeconomic considerations include lack of access to physicians, medications, and other health care resources. For example, in 1993, whites had a significantly higher rate of visits to physicians than did blacks (3.0 and 1.8 visits per person per year, respectively).*
- Low socioeconomic status, low levels of formal education, and exposure to violence lessen the success of antihypertensive therapy.†
- Uncontrolled severe hypertensives are more likely to be current smokers, and smoking, as a marker of poor health behavior, is associated with reduced compliance with medications.

*Data from the National Ambulatory Medical Care Survey: 1993 Summary. Vital and Health Statistics. U.S. Department of Health and Human Services, DHHS Publication No. (PHS) 98-1797, April 1998.

†Data from Shea S, Misra D, Ehrlich, et al: Predisposing factors for severe, uncontrolled hypertension in an inner-city minority population. N Engl J Med 1992;327:776-81.

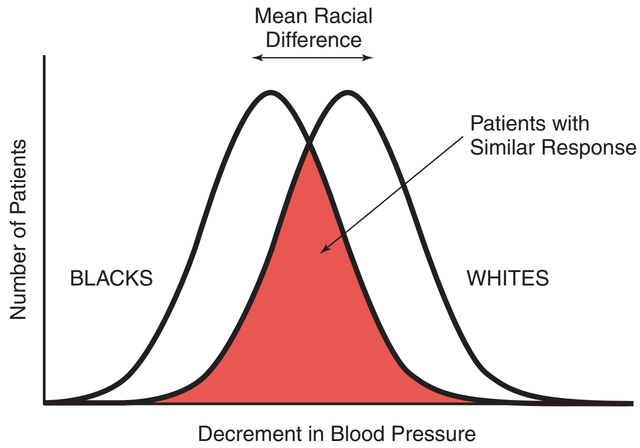

Figure 31–1 Decrement in blood pressure among whites and blacks after administration of antihypertensive drug. Red area represents whites and blacks who have similar responses. (Modified from Sehgal AR: Overlap between whites and blacks in response to antihypertensive drugs. Hypertension 2004;43:566-72.)

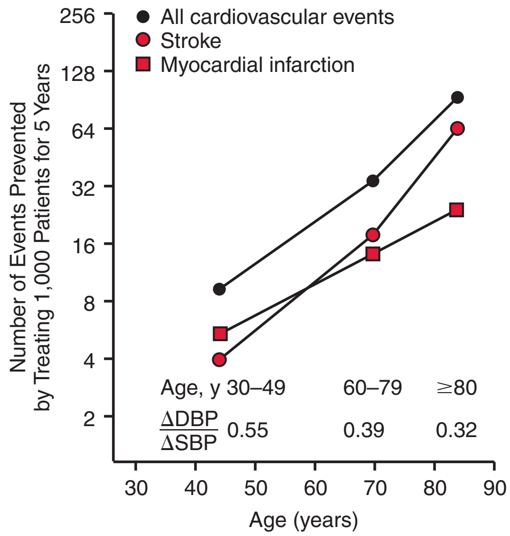

Figure 31–2 Absolute benefits in the prevention of fatal and nonfatal cardiovascular events, stroke, and myocardial infarction in three age groups. Symbols represent the number of events that can be prevented by treating 1000 patients for 5 years. ΔDBP/ΔSBP refers to the mean ratio of DBP-to-SBP lowering; y, years. (Modified from Wang JG, Staessen JA, Franklin SS, et al: Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. Hypertension 45:907-913, 2005.)

that may influence treatment choices. Blacks as a group respond somewhat less well than whites to monotherapy with β-blockers and ACE inhibitors, perhaps because they tend to have a salt-sensitive, low-renin form of hypertension.[162] Higher-than-conventional doses of an ACE inhibitor may improve the BP response in these patients, however.[65] Blacks and whites generally respond equally well to diuretics, CCBs, and peripheral α-blockers. To achieve adequate BP control, a diuretic is required more often in blacks than in whites. The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for HF including neurohormonal blockers is efficacious and increases survival among black patients with advanced HF.[163] Because hydralazine and isosorbide dinitrate in tandem increase nitric oxide bioavailability, the presumption has been that such changes explain the observed positive outcomes in these studies.

Elderly Patients

The elderly (aged 65 years and older) represent a growing proportion of the U.S. population, and hypertension is the single-most important remedial risk factor for CVD in this group. Both systolic and diastolic BP increase with age, although there is a disproportionate increase in systolic BP, which continues to rise until the eighth or ninth decade, whereas diastolic BP tends to stabilize by the age of 60 and decline thereafter. Systolic hypertension in the elderly involves increases in arterial stiffness and early wave reflections, both of which cause a predominant or selective increase in systolic BP.[164] This disproportionate rise in systolic BP produces a widened pulse pressure and isolated systolic hypertension (ISH). The Framingham Heart Study, among others, has clearly shown that ISH is a major risk factor for cardiovascular death in elderly persons.[165] Moreover, clinical trials have repeatedly shown the benefits of BP control for prevention of stroke and dementia of both the multi-infarct and Alzheimer subtypes.[166] However, the best choice of individual antihypertensive agents and combinations of agents in the elderly hypertensive remains controversial.

Anatomic and humoral changes that occur with aging dictate that special attention be paid to the clinical assessment and treatment of hypertension in the elderly. Clinical assessment of ISH is often confounded by a widened auscultatory gap, which may lead to underestimation of systolic BP. Therefore it is important to inflate the cuff to at least 250 mm Hg when measuring BP in elderly persons. Elderly persons are prone to the development of *pseudohypertension,* a phenomenon related to calcified, noncompressible arteries, in which cuff BP can significantly overestimate true intra-arterial BP. This finding can be diagnosed by manually inflating the BP cuff above systolic BP, whereupon brachial or radial artery pulses should be obliterated. If these arteries remain palpable, a positive Osler's sign, the patient likely has a component of pseudohypertension. As an example of this, 7.2% (243 of 3387) of SHEP patients were determined to be Osler maneuver positive.[167] In the elderly, it is also important to test for orthostatic hypotension both before and during therapy. Failure to detect this condition may result in potentially life-threatening consequences.

The once-common notion that ISH is a physiologic consequence of aging that preserves organ perfusion and does not require treatment has been dispelled by results of randomized controlled trials (Fig. 31–2).[46,168-170] For example, the SHEP and Syst-EUR trials have clearly documented the benefits of BP control in elderly patients.[46,169] Reducing BP in elderly hypertensive persons has obvious survival benefits, and treatment of ISH in older patients with SBP of at least 160 mm Hg is supported by strong evidence. The evidence to support treatment of ISH patients to a goal of 140 mm Hg or those with baseline SBP of 140 to 159 mm Hg is less strong. These treatment decisions should be more sensitive to patient preferences and tolerance of therapy.[171]

The process of initiating treatment remains a challenge and is not without the risk of significant neurologic and constitutional side effects. It is appropriate to initiate treatment with lower doses of antihypertensive agents and to bring BP down slowly, monitoring for orthostatic hypotension, impaired cognition, and electrolyte abnormalities. Diuretics decrease cerebrovascular and CVD events and can be used as first-line therapy in the elderly.[46,172] β-Blockers may be less effective in elderly patients and have not been shown to reduce all-cause mortality rates.[33-35] Central α-agonists and peripheral α-antagonists often result in troubling side effects, such as dry mouth and orthostatic hypotension, and therefore should be used with particular care in elderly patients. CCBs, ACE inhibitors, and ARBs can be used, and the latter two classes often can be successfully combined with a diuretic. Low-dose combination therapy is well suited for this population and offers the advantages of reducing the risk of dose-dependent side effects and decreasing the number of pills that need to be taken.[37,173]

Step-Down Therapy

An effort to decrease the number or dosage of antihypertensive medications, or both, should be considered after hypertension has been effectively controlled for at least 1 year.[174] This should be done in a deliberate, slow, and progressive manner. The Trial of Nonpharmacologic Interventions in the Elderly (TONE) demonstrated that dietary Na^+ restriction (reducing intake by 40 mmol) or weight 1oss (≈3.5-kg), or both, in older patients without evidence of CVD and with BP < 150/90 mm Hg permitted the safe discontinuation of antihypertensive medication.[175] However, continued surveillance on the part of the physician is necessary for these patients because BP not uncommonly rises again to hypertensive levels, sometimes months or years after medication discontinuation, particularly when previously successful lifestyle modifications are not sustained.[175]

CHOICE OF DRUGS: FIRST, SECOND, AND BEYOND

A number of algorithms have been put together for the treatment of hypertension. Such algorithms at best offer simple guidelines for treatment. Treatment guidelines are most helpful when a population-based approach to therapy is sought. They are of lesser usefulness when the clinician is called on to choose a starting medication for the individual

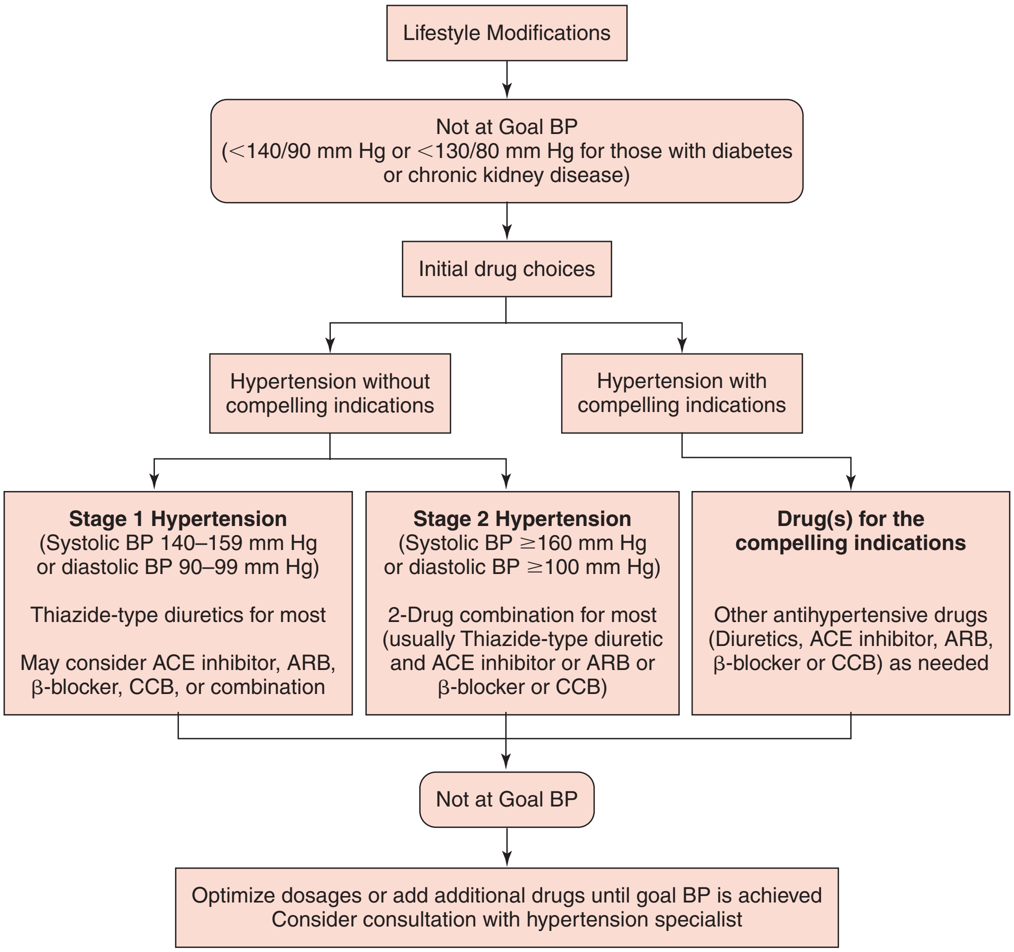

Figure 31–3 Hypertension treatment algorithm. (Modified from Chobanian AV, Bakris GL, Black HR, et al, for the NHLBI Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003;289:2560-72.)

patient. The individual patient should receive customized therapy whenever possible. Clinical trial results indicate that many hypertensive patients require multidrug therapy to achieve goal BP, particularly if systolic BP values < 130 mm Hg are being sought.[5] A practical approach to achieving BP control is to rely on low-dose combinations of antihypertensive medications given either as fixed-dose combinations or one drug sequentially added to the other.[176] This approach, advanced by JNC-7, takes advantage of the well-established additive or synergistic effects of various combinations of drugs (Fig. 31–3).[5]

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Secondary Hypertension: Endocrine Causes

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CHAPTER CONTENTS

Hypertension may be the initial presentation of many endocrine disorders (Table 32–1). Although endocrine causes of hypertension are uncommon, an accurate diagnosis provides clinicians with a unique treatment opportunity, that is, to render a surgical cure or to achieve a dramatic response with pharmacologic therapy.[1] The therapeutic approaches to endocrine disorders—ranging from the classic adrenal causes of hypertension (e.g., pheochromocytoma and primary aldosteronism) to pituitary-dependent hypertension (e.g., Cushing's syndrome and acromegaly)—are reviewed in this chapter.

PHEOCHROMOCYTOMA

Catecholamine-producing tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia are termed *pheochromocytomas* and *catecholamine-secreting paragangliomas* (or *extra-adrenal pheochromocytomas*), respectively. Because clinical presentations of these disorders and the therapeutic approaches to them are similar, the term *pheochromocytoma* is used to refer to both adrenal pheochromocytomas and catecholamine-secreting paragangliomas.

Presentation

Although catecholamine-secreting tumors are rare (annual incidence of 2 to 8 cases per 1 million people),[1a] it is important to suspect, confirm, localize, and resect these tumors because (1) the associated hypertension is curable with surgical removal of the tumor; (2) the risk of a lethal paroxysm exists; (3) at least 10% of the tumors are malignant; and (4) 10% to 20% are familial, and detection of this tumor in the proband may result in early diagnosis in other family members. These tumors occur with equal frequency in men and women, primarily in the third, fourth, and fifth decades. Patients harboring catecholamine-secreting tumors may be asymptomatic and present with an incidentally discovered adrenal mass on computerized imaging.[2] However, symptoms are usually present and due to the pharmacologic effects of excessive levels of catecholamines or cosecreted peptide hormones (Table 32–2).[3] The resultant hypertension may be sustained or paroxysmal. Episodic symptoms may occur in spells, or paroxysms, that can be extremely variable in presentation.

Syndromic Pheochromocytoma

Approximately 10% to 20% of patients with catecholamine-secreting tumors have associated germline mutations (inherited mutations present in all cells of the body) in genes known to cause genetic disease.[4,5] The familial neurocristopathic syndromes associated with adrenal pheochromocytoma include multiple endocrine neoplasia (MEN) type 2A (pheochromocytoma, medullary thyroid carcinoma, and hyperparathyroidism) and type 2B (MEN 2B) (pheochromocytoma, medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, intestinal ganglioneuromatosis, and marfanoid body habitus); neurofibromatosis type 1 (NF1); von Hippel-Lindau disease (VHL) (pheochromocytoma, retinal angiomas, cerebellar hemangioblastoma, renal and pancreatic cysts, and renal cell carcinoma); familial pheochromocytoma (specific mutations yet to be identified); and familial paraganglioma. Another syndrome associated with catecholamine-secreting tumors that does not appear to be inherited is the Carney triad (gastric leiomyosarcoma, pulmonary chondroma, and extra-adrenal pheochromocytoma).[6]

Familial paraganglioma is an autosomal dominant disorder characterized by paragangliomas that are located most often in the head and neck, but they also have been found in the thorax, abdomen, adrenal medulla, pelvis, and urinary bladder. The occurrence of catecholamine hypersecretion in familial paraganglioma depends on tumor location; approximately 5% of head and neck paragangliomas and 50% of abdominal paragangliomas are hormone-producing tumors.[7] Familial paraganglioma is caused by mutations in the succinate dehydrogenase (SDH; succinate-ubiquinone oxidoreductase) subunit genes *SDHB*, *SDHC*, *SDHD*, which comprise portions of mitochondrial complex II.[8,9] *SDHB* mutations have been associated with increased risk of malignant paraganglioma.[9,10]

Diagnosis

The diagnostic approach to catecholamine-producing tumors is divided into two series of studies (Fig. 32–1). First, the diagnosis of a catecholamine-producing tumor must be suspected and then confirmed biochemically by increased concentrations of fractionated catecholamines and metanephrines in the urine or plasma. The 24-hour urinary excretion rates of

Table 32–1 Endocrine Causes of Hypertension

Adrenal Dependent
Pheochromocytoma
Primary aldosteronism
Hyperdeoxycorticosteronism
Congenital adrenal hyperplasia
11β-Hydroxylase deficiency
17α-Hydroxylase deficiency
Deoxycorticosterone-producing tumor
Primary cortisol resistance
Cushing's syndrome
Apparent Mineralocorticoid Excess (AME)/ 11β-Hydroxysteroid Dehydrogenase Deficiency
Genetic
Type 1 AME
Type 2 AME
Acquired
Licorice or carbenoxolone ingestion (type 1 AME)
Cushing's syndrome (type 2 AME)
Thyroid Dependent
Hypothyroidism
Hyperthyroidism
Parathyroid Dependent
Hyperparathyroidism
Pituitary Dependent
Acromegaly
Cushing's syndrome

Table 32–2 Signs and Symptoms Associated with Catecholamine-Secreting Tumors

Spell Related
Headache
Palpitations
Diaphoresis
Epigastric and chest pain
Pallor
Nausea
Dyspnea
Anxiety
Hypertension
Tremor
Chronic
Hypertension
Orthostatic hypotension
Grade II to IV retinopathy
Tremor
Fever
Weight loss
Congestive heart failure—dilated or hypertrophic cardiomyopathy
Hyperglycemia
Constipation
Painless hematuria (associated with urinary bladder paraganglioma)
Ectopic hormone secretion-dependent symptoms (e.g., CRH/ACTH, GHRH, PTH-RP, VIP)
Not Typical of Pheochromocytoma
Flushing

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GHRH, growth hormone–releasing hormone; PTH-RP, parathyroid hormone-related peptide; VIP, vasoactive intestinal polypeptide.
Modified from Young WF Jr: Pheochromocytoma: 1926-1993. Trends Endocrinol Metab 1993;4:122-7.

catecholamines (norepinephrine, epinephrine, and dopamine) and fractionated metanephrines are the tests of choice to screen for catecholamine-secreting tumors (see Fig. 32–1).[11] Measurement of the concentrations of plasma fractionated metanephrines is also useful in screening for pheochromocytoma.[11,12]

The next step is to localize the catecholamine-producing tumor to guide the surgical approach. Computer-assisted adrenal and abdominal imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) is the first localization test. About 98% of these tumors are in the abdomen, with approximately 90% of them in the adrenal glands.[13] If the findings on abdominal imaging are negative, scintigraphic localization with [^{123}I]metaiodobenzylguanidine (^{123}I-MIBG) is indicated. Thorough discussions of the diagnostic investigation of catecholamine-producing tumors may be found elsewhere.[14]

Principles of Treatment

The treatment of choice for pheochromocytoma is surgical resection. Most of the tumors are benign and can be excised totally. However, preoperatively, the chronic and acute effects of excess circulating catecholamines should be reversed.

Preoperative Management

Combined α- and β-adrenergic blockade is required preoperatively to control blood pressure and to prevent intraoperative hypertensive crises. α-Adrenergic blockade should be started 7 to 10 days preoperatively to allow expansion of the contracted blood volume. A liberal salt diet is advised during the preoperative period. After adequate α-adrenergic blockade has been achieved, β-adrenergic blockade is initiated, usually about 3 days preoperatively. Echocardiography performed preoperatively may be helpful in detecting catecholamine cardiomyopathy.

α-Adrenergic Blockade

Phenoxybenzamine is an irreversible, long-acting, α-adrenergic blocking agent (Table 32–3). The effects of daily administration are cumulative for nearly a week, and approximately 25% of an oral dose is absorbed. Phenoxybenzamine is available in 10-mg capsules. The initial dosage is 10 mg orally one to two times a day, and the dosage is increased by 10 to 20 mg every 2 to 3 days as needed to control the blood pressure and spells. The average dosage is 20 to 100 mg/day. The target blood pressure is less than 120/80 mm Hg seated, with systolic blood pressure greater than 90 mm Hg standing. These target blood

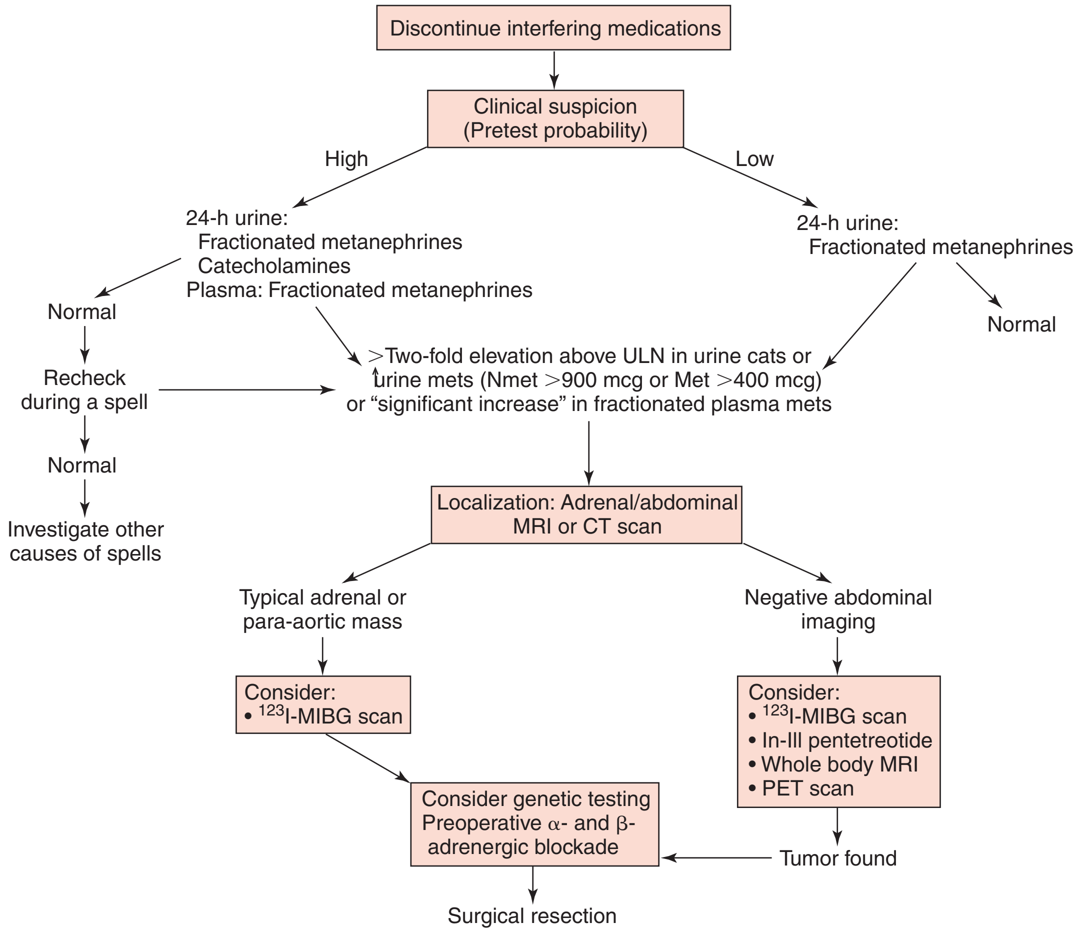

Figure 32–1 Evaluation and treatment of catecholamine-producing tumors. Clinical suspicion is triggered by the following: paroxysmal symptoms (especially hypertension); hypertension that is intermittent, unusually labile, or resistant to treatment; family history of pheochromocytoma or associated conditions; or incidentally discovered adrenal mass. See text for details. CT, computed tomography; ^{123}I-MIBG, ^{123}I-metaiodobenzylguanidine; MRI, magnetic resonance imaging. (Modified from Young WF Jr: Pheochromocytoma: 1926-1993. Trends Endocrinol Metab 1993;4:122-7.)

pressure readings may be modified on the basis of age and comorbid disease. Side effects include postural hypotension, tachycardia, miosis, nasal congestion, inhibition of ejaculation, diarrhea, and fatigue. Prazosin, terazosin, and doxazosin are selective α_1-adrenergic blocking agents. Because these agents have a more favorable side effect profile, they may be preferable to phenoxybenzamine when long-term pharmacologic treatment is indicated (e.g., for mild metabolically active metastatic pheochromocytoma). However, phenoxybenzamine is the drug preferred for preoperative preparation because it provides α-adrenergic blockade of long duration. Effective α-adrenergic blockade permits expansion of blood volume, which is usually severely decreased because of excessive adrenergic vasoconstriction.

β-Adrenergic Blockade

A β-adrenergic antagonist should be administered only after α-adrenergic blockade is effective because β-adrenergic blockade alone may increase the severity of the hypertension through unopposed α-adrenergic stimulation. Preoperative β-adrenergic blockade is indicated to control the tachycardia associated with both the high concentrations of circulating catecholamines and the α-adrenergic blockade. Caution is indicated if the patient has asthma or congestive heart failure. A chronic excess level of catecholamines can produce myocardiopathy, and β-adrenergic blockade can result in acute pulmonary edema. Noncardioselective β-adrenergic blockers, such as propranolol and nadolol, or cardioselective β-adrenergic blockers, such as atenolol and metoprolol, may be used. Mechanisms of action, routes of metabolism, dosages, and side effects of β-adrenergic blockers are discussed in Chapter 5. When initiating treatment with a β-adrenergic blocker, the drug should be started at a low dose. For example, propranolol is usually started at a dose of 10 mg orally every 6 hours at least 4 to 7 days after the initiation of α-adrenergic blockade. The dose is increased as needed to control the tachycardia.

Labetalol exhibits both selective α_1-adrenergic and nonselective β-adrenergic blocking activities in a ratio of approximately 1:3 (see Table 32–3). Paradoxical hypertensive responses in patients with pheochromocytoma treated with labetalol have been reported, presumably because of incomplete α-adrenergic blockade. Therefore, the safety of labetalol as primary therapy is controversial.

Table 32–3 Orally Administered Drugs Used to Treat Pheochromocytoma

Drug	Dosage, mg/d* Initial—Maximum	Side Effects
α-Adrenergic blocking agents		
Phenoxybenzamine	20†-100†	Postural hypotension, tachycardia, miosis, nasal congestion, diarrhea, inhibition of ejaculation, fatigue
Prazosin	1-20‡	First-dose effect, dizziness, drowsiness, headache, fatigue, palpitations, nausea
Terazosin	1-20†	First-dose effect, asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations, somnolence
Doxazosin	1-20	First-dose effect, orthostasis, peripheral edema, fatigue, somnolence
Combined α- and β-adrenergic blocking agent		
Labetalol	200†-1200†	Dizziness, fatigue, nausea, nasal congestion, impotence
Calcium Channel Blockers		
Nicardipine sustained release	60-120†	Edema, dizziness, headache, flushing, nausea, dyspepsia
Catecholamine Synthesis Inhibitor		
α-Methyl—*p*-L-tyrosine (metyrosine)	1000‡-4000‡	Sedation, diarrhea, anxiety, nightmares, crystalluria, galactorrhea, extrapyramidal symptoms

*Given once daily unless otherwise indicated.
†Given in two doses daily.
‡Given in three or four doses daily.

Catecholamine Synthesis Inhibitor

Rarely, α- and β-adrenergic blocking agents may be ineffective or poorly tolerated, and an alternative medical approach is necessary. α-Methyl-*p*-L-tyrosine (metyrosine) inhibits the synthesis of catecholamines by blocking the enzyme tyrosine hydroxylase. Metyrosine is absorbed rapidly from the gastrointestinal tract, and most of it is excreted unchanged in the urine. Metyrosine is available as 250-mg capsules (see Table 32–3). The initial dosage is 250 mg orally four times a day. The dosage may be increased by 500 mg/day, every 1 or 2 days, to a maximum of 4 g/d (1 g four times per day) as needed for blood pressure control. Side effects include sedation, somnolence, depression, diarrhea, anxiety, nightmares, crystalluria and urolithiasis, galactorrhea, and extrapyramidal manifestations. Therefore, this agent should be used only after other agents have been ineffective. The extrapyramidal effects of phenothiazines or haloperidol may be potentiated, and their concomitant use with metyrosine should be avoided. High fluid intake to avoid crystalluria is suggested for any patient taking more than 2 g daily. Metyrosine is especially useful for patients who, for cardiopulmonary reasons, cannot be treated with combined α- and β-adrenergic blockade.

Calcium Channel Blockers

Calcium channel blockers, which block norepinephrine-mediated calcium transport into vascular smooth muscle, have been used successfully at several medical centers to preoperatively prepare patients with pheochromocytoma.[15-17] Nicardipine is the most commonly used calcium channel blocker in this setting. Nicardipine is given orally to control blood pressure preoperatively and is given as an intravenous infusion intraoperatively. When calcium channel blockers are used as the primary mode of antihypertensive therapy, they appear to be just as effective as α- and β-adrenergic blockade.

Acute Hypertensive Crises

Acute hypertensive crises may occur before or during surgery and should be treated with nitroprusside, phentolamine, or nicardipine administered intravenously (Table 32–4) (see Chapter 5). Phentolamine is a short-acting, nonselective α-adrenergic blocker available in lyophilized form in 5-mg vials. An initial test dose of 1 mg is administered and, if necessary, followed by repeat 5-mg boluses or continuous infusion. The response to phentolamine is maximal in 2 to 3 minutes after a bolus injection and lasts 10 to 15 minutes. Nicardipine infusion is initiated at 5.0 mg/hr, and the infusion rate may be increased by 2.5 mg/hr every 15 minutes up to a maximum of 15.0 mg/hr. The use of nitroprusside is discussed later.

Anesthesia and Surgery

Resection of a catecholamine-secreting tumor is a high-risk surgical procedure, and an experienced surgeon/anesthesiologist team is required. The last oral doses of α- and β-adrenergic blockers can be administered orally early in the morning on the day of the operation. Fentanyl, ketamine, and morphine should be avoided because they can potentially stimulate catecholamine release from a pheochromocytoma.[18] Also, parasympathetic nervous system blockade with atropine should be avoided because of the associated tachycardia. Anesthesia may be induced with intravenous injection of propofol, etomidate, or barbiturates in combination with synthetic opioids.[18] Most anesthetic gases can be used, but halothane and desflurane should be avoided. Cardiovascular and hemodynamic variables must be monitored closely. Continuous measurement of intra-arterial pressure and heart rhythm is required. If the patient has congestive heart failure or decreased cardiac

Table 32–4 Intravenously Administered Drugs Used to Treat Pheochromocytoma

Agent	Dosage Range
For Hypertension	
Phentolamine	1 mg IV test dose, then 2- to 5-mg IV boluses as needed or continuous infusion.
Nitroprusside	Infusion rates of 2 mcg/kg/min are suggested as safe, whereas rates greater than 4 mcg/kg/min may lead to cyanide toxicity within 3 hr. Doses exceeding 10 mcg/kg/min are rarely required, and the maximal dose should not exceed 800 mcg/min.
Nicardipine	Initiate therapy at 5.0 mg/hr, and the infusion rate may be increased by 2.5 mg/hr every 15 min up to a maximum of 15.0 mg/hr.
For Cardiac Arrhythmia	
Lidocaine	Initiate therapy with a bolus of 1 to 1.5 mg/kg (75 to 100 mg); additional boluses of 0.5 to 0.75 mg/kg (25-50 mg) can be given every 5 to 10 minutes if needed up to a maximum of 3 mg/kg. Loading is followed by a maintenance infusion of 2 to 4 mg/min (30 to 50 mcg/kg/min) adjusted for effects and settings of altered metabolism (e.g., heart failure, liver congestion) and as guided by blood level monitoring.
Esmolol	An initial loading dose of 0.5 mg/kg is infused over a minute duration followed by a maintenance infusion of 0.05 mg/kg/min for the next 4 min. Depending on the desired ventricular response, the maintenance infusion may then be continued at 0.05 mg/kg/min or increased stepwise (e.g., by 0.1 mg/kg/min increments to a maximum of 0.2 mg/kg/min) with each step being maintained for 4 or more min.

IV, intravenous.

reserve, monitoring of pulmonary capillary wedge pressure is indicated. Surgical survival rates are 98% to 100%.[19] The preoperative and perioperative treatment approaches outlined here are the same for adults and children.[20,21]

In the past, an anterior midline abdominal surgical approach was generally used for resecting adrenal pheochromocytoma. However, the laparoscopic approach to the adrenal gland is currently the procedure of choice for patients with solitary intra-adrenal pheochromocytomas that are less than 8 to 10 cm in diameter.[22] The average length of hospitalization for patients who undergo laparoscopic adrenalectomy for pheochromocytoma is 1.7 to 2.3 days.[23,24] If the pheochromocytoma is in the adrenal gland, the entire gland should be removed. Laparoscopic adrenalectomy for pheochromocytoma should be converted to open adrenalectomy for difficult dissection, invasion, adhesions, or surgeon inexperience.[25] If the tumor is malignant, as much of the tumor should be removed as possible. If a bilateral adrenalectomy is planned preoperatively, the patient should receive glucocorticoid stress coverage while awaiting transfer to the operating room. Glucocorticoid coverage should be initiated in the operating room if unexpected bilateral adrenalectomy is necessary. Cortical-sparing bilateral adrenalectomies have been used to treat patients with MEN 2 and VHL disease.[26] However, with MEN 2 patients, there is a concern of leaving residual adrenal medullary tissue behind and thus increasing the risk of recurrent pheochromocytoma. An anterior midline abdominal surgical approach is indicated for abdominal paragangliomas. Paragangliomas of the neck, chest, and urinary bladder require specialized approaches.

Hypotension may occur after surgical resection of the pheochromocytoma, and it should be treated with fluids and small, intermittent doses of intravenous pressor agents. Postoperative hypotension is less frequent in patients who have had adequate preoperative α-adrenergic blockade. If both adrenal glands were manipulated during surgery, adrenocortical insufficiency should be considered a potential cause of postoperative hypotension. Because hypoglycemia can occur in the immediate postoperative period, blood glucose levels should be monitored and fluid given intravenously should contain 5% dextrose.

Blood pressure is usually normal by the time of hospital discharge, but some patients remain hypertensive for up to 4 to 8 weeks postoperatively. Long-standing, persistent hypertension does occur and may be related to inadvertent ligation of a polar renal artery, resetting of baroreceptors, hemodynamic changes, structural changes of the blood vessels, altered sensitivity of the vessels to pressor substances, functional or structural renal changes, or coincident primary hypertension.

Long-Term Postoperative Follow-up

Approximately 1 to 2 weeks after surgery, catecholamines and metanephrines should be measured by collecting a 24-hour urine specimen. If the levels are normal, the resection of the pheochromocytoma should be considered complete. The survival rate after removal of a benign pheochromocytoma is nearly that of age- and sex-matched normal controls. Increased levels of catecholamines and metanephrines detected postoperatively are consistent with residual tumor, either a second primary lesion or occult metastases. If bilateral adrenalectomy was performed, lifelong glucocorticoid and mineralocorticoid replacement therapy is prescribed. Twenty-four hour urinary excretion of catecholamines and fractionated metanephrines or fractionated plasma metanephrines should be checked annually for life. Annual biochemical testing assesses for metastatic disease, tumor recurrence in the adrenal bed, or delayed appearance of multiple primary tumors. Recurrence rates are highest for patients with familial disease, right-sided adrenal pheochromocytoma, or paraganglioma.[27] Follow-up CT or MRI is not necessary unless the metanephrines or catecholamine levels, or both, become elevated or the original tumor was associated with minimal catecholamine excess.

Genetic testing should be considered for patients with one or more of the following: a family history of pheochromocy-

toma, paraganglioma, or any sign that suggests a genetic cause (e.g., retinal angiomas, axillary freckling, café-au-lait spots, cerebellar tumor, medullary thyroid carcinoma (MTC), hyperparathyroidism).[28] In addition, all first-degree relatives of a patient with pheochromocytoma or paraganglioma should have biochemical testing (e.g., 24-hr urine for fractionated metanephrines and catecholamines). If mutation testing in a patient is positive, first-degree relatives should have stepwise (e.g., parents first) germline screening.

Malignant Pheochromocytoma

Distinguishing between benign and malignant catecholamine-secreting tumors on the basis of clinical, biochemical, or histopathologic characteristics is difficult.[29] Malignancy is rare in patients with a familial adrenal syndrome but common in those with familial paraganglioma caused by mutations in *SDHB*. Although the mean 5-year survival rate for patients with malignant pheochromocytoma is less than 50%, the prognosis is variable: Approximately 50% of patients have an indolent form of the disease, with a life expectancy of more than 20 years, and the other 50% have rapidly progressive disease, with death occurring within 1 to 3 years. Metastatic sites include local tissue, liver, bone, lung, and lymph nodes. Metastatic lesions should be resected if possible. Skeletal metastatic lesions that are painful or threaten structural function can be treated with external radiotherapy or cryoablation therapy. External radiotherapy can also be used to treat unresectable soft tissue lesions.

Local tumor irradiation with therapeutic doses of ^{131}I-MIBG has produced partial and temporary responses in approximately one third of patients.[30-33] Thrombotic therapy for large, unresectable liver metastases and radiofrequency ablation for small liver metastases are options to be considered. In selected cases, long-acting octreotide has been beneficial. If the tumor is considered aggressive and the patient's quality of life is affected, combination chemotherapy may be considered.[34] Management of a patient who has malignant pheochromocytoma can be frustrating because curative options are limited. Clearly, innovative prospective protocols are necessary to seek new treatment options for this neoplasm.[29]

Pheochromocytoma in Pregnancy

Pheochromocytoma in pregnancy can cause the death of both the fetus and the mother.[35] The treatment of hypertensive crises is the same as that for nonpregnant patients except that nitroprusside should be avoided in the pregnant patient. Although some controversy exists about the most appropriate management, pheochromocytomas should be removed immediately if diagnosed during the first two trimesters of pregnancy. The preoperative preparation is the same as that for nonpregnant patients. If medical therapy is chosen or if the patient is in the third trimester, cesarean section and removal of the pheochromocytoma in the same operation are indicated. Spontaneous labor and delivery should be avoided.

PRIMARY ALDOSTERONISM

Hypertension, hypokalemia, suppressed plasma renin activity (PRA), and increased aldosterone excretion characterize the syndrome of primary aldosteronism, which was first described in 1955.[36] Bilateral idiopathic hyperaldosteronism (IHA) and aldosterone-producing adenoma (APA) are the most common subtypes of primary aldosteronism (Table 32–5). A much less common form, unilateral hyperplasia or primary adrenal hyperplasia, is caused by zona glomerulosa hyperplasia of predominantly one adrenal gland. Two forms of familial hyperaldosteronism (FH) have been described: FH type I and FH type II. FH type I, or glucocorticoid-remediable aldosteronism (GRA), is autosomal dominant in inheritance and associated with varying degrees of hyperaldosteronism, high levels of hybrid steroids (e.g., 18-hydroxycortisol and 18-oxocortisol), and suppressability with exogenous glucocorticoids. FH type II refers to the familial occurrence of APA or IHA, or both.

Table 32–5 Subtypes of Primary Aldosteronism

Aldosterone-producing adenoma (APA)
Idiopathic hyperaldosteronism (IHA)
Primary adrenal hyperplasia (PAH) (unilateral adrenal hyperplasia)
Aldosterone-producing adrenocortical carcinoma
Ectopic aldosterone-producing (e.g., ovarian tumor)
Familial hyperaldosteronism (FH)
Glucocorticoid-remediable aldosteronism (FH type 1)
FH type 2 (APA or IHA, or both)

Modified from Young WF Jr, Hogan MJ: Renin-independent hypermineralocorticoidism. Trends Endocrinol Metab 1994;5:97-106.

Diagnosis

Screening

In the past, clinicians would not consider the diagnosis of primary aldosteronism unless the patient presented with spontaneous hypokalemia, and then the diagnostic evaluation would require discontinuing antihypertensive medications for 2 weeks. The "spontaneous hypokalemia/no antihypertensive drug" diagnostic approach resulted in predicted primary aldosteronism prevalence rates of <0.5% of hypertensive patients.[37,38] However, it is now recognized that most patients with primary aldosteronism are not hypokalemic and present with asymptomatic hypertension, which may be mild or severe.[39] When hypokalemia does occur, it may be associated with nocturia, polyuria, muscle cramps, or palpitations. Screening can be completed with a simple morning (8 to 10 A.M.) blood test (plasma aldosterone concentration [PAC]–to–plasma renin activity [PRA] ratio) in a seated ambulant patient.[40] The patient may take any antihypertensive drugs except aldosterone-receptor blockers and high-dose amiloride (spironolactone and eplerenone should be discontinued 4 to 6 weeks before testing for primary aldosteronism). Hypokalemia is associated with false-negative ratios, and any potassium deficit should be corrected before testing. Although there is some uncertainty about test characteristics and lack of standardization, the PAC-PRA ratio is widely accepted as the screening test of choice for primary aldosteronism.

The use of the PAC-PRA ratio as a screening test followed by aldosterone suppression confirmatory testing has resulted in much higher prevalence estimates (5%-13% of all hypertensives) for primary aldosteronism.[39] The prevalence of primary

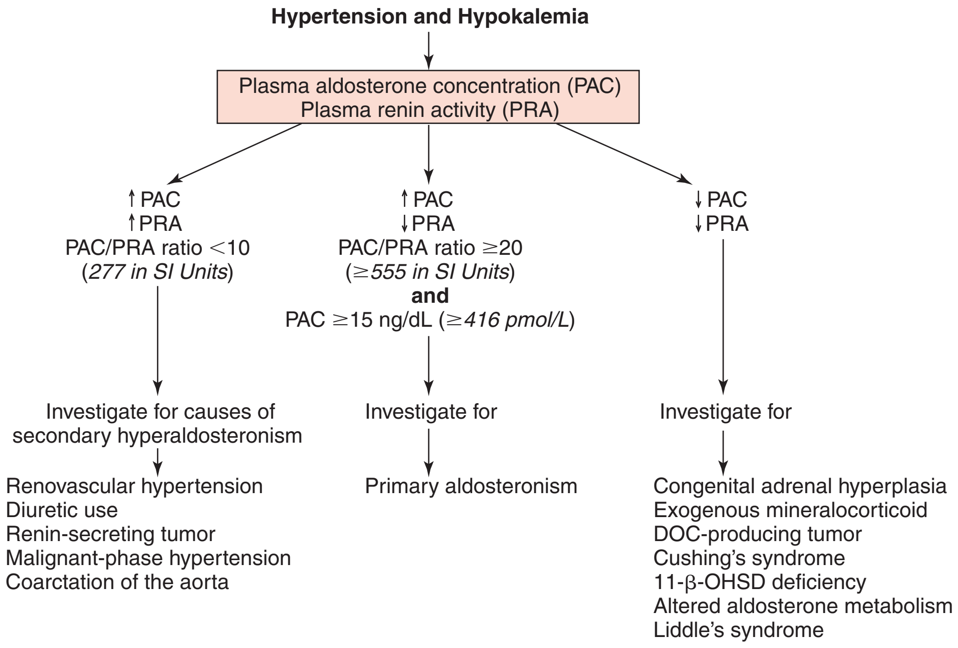

Figure 32–2 Use of the plasma aldosterone concentration (PAC)–to–plasma renin activity (PRA) ratio to differentiate among different causes of hypertension and hypokalemia. DOC, deoxycorticosterone; OHSD, hydroxysteroid dehydrogenase. (Modified from Young WF Jr, Hogan MJ: Renin-independent hypermineralocorticoidism. Trends Endocrinol Metab 1994;5:97-106.)

aldosteronism approaches 20% in patients with resistant hypertension.[41] Patients with hypertension and hypokalemia, regardless of presumed cause (e.g., diuretic treatment), and most patients with treatment-resistant hypertension should undergo screening for primary aldosteronism with a PAC-PRA ratio (cutoff is laboratory dependent) (Fig. 32–2).[42] A high PAC-PRA ratio is a positive screening test result, a finding that warrants confirmatory testing.

Confirming the Diagnosis

Confirmatory testing is completed with sodium suppression testing [oral sodium loading, saline suppression test, or fludrocortisone (Florinef) suppression testing].[43] At the Mayo Clinic, we prefer the high-sodium diet for 3 to 4 days with 24-hour urine collection (days 3 to 4) for aldosterone, sodium, and creatinine.[43] When the 24-hour urinary sodium is >200 mEq (confirming adequate sodium loading), patients with primary aldosteronism demonstrate autonomous aldosterone production with urinary aldosterone levels >12 mcg/24-hour. During the oral sodium loading, it is important to monitor serum electrolytes and blood pressure daily and increase potassium supplementation and antihypertensive medications as indicated.

Subtype Evaluation

Unilateral adrenalectomy in patients with APA or PAH results in normalization of hypokalemia in all; hypertension is improved in all and is cured in approximately 30% to 60% of these patients. In IHA, unilateral or bilateral adrenalectomy seldom corrects the hypertension. IHA and GRA should be treated medically. Therefore for those patients who want to pursue a surgical cure, accurate distinction among the subtypes of primary aldosteronism is a critical step (Fig. 32–3). The subtype evaluation may require one or more tests, the first of which is imaging the adrenal glands with computed tomography (CT) (see Fig. 32–3). When a solitary hypodense (Hounsfield unit score <10 HU) unilateral macroadenoma (>1 cm) and normal contralateral adrenal morphology are found on CT in a young patient (<40 years) with primary aldosteronism, unilateral adrenalectomy is a reasonable therapeutic option. However, in many cases, CT may show normal-appearing adrenals, minimal unilateral adrenal limb thickening, unilateral microadenomas (≤1 cm), or bilateral macroadenomas. We have found in 203 patients, who were evaluated with both CT and adrenal vein sampling, that CT accurately distinguished APA from IHA in only 53% of patients.[44] Small APAs may be labeled incorrectly as "IHA" on the basis of CT findings of bilateral nodularity or normal-appearing adrenals. Also, apparent adrenal microadenomas may represent areas of hyperplasia, and unilateral adrenalectomy would be inappropriate. In addition, nonfunctioning unilateral adrenal macroadenomas are not uncommon, especially in older patients (>40 years).

Patients with APAs have more severe hypertension, more frequent hypokalemia, higher plasma (>25 ng/dL; >694 pmol/L) and urinary (>30 mcg/24 hour; >83 nmol/d) levels of aldosterone, and are younger (<50 years) than those with IHA. Patients fitting these descriptors are considered to have a "high probability of APA" (see Fig. 32–3). However, these factors are not absolute predictors of unilateral versus bilateral adrenal disease. Adrenal venous sampling (AVS) is a difficult procedure because the right adrenal vein is both small and difficult to cannulate; the success rate depends on the proficiency of the angiographer.[43,44] A practical approach is the selective use of AVS as outlined in Figure 32–3.

Principles of Treatment

The treatment goal is to prevent the morbidity and mortality associated with hypertension, hypokalemia, and cardiovascular damage. The cause of the primary aldosteronism helps to determine the appropriate treatment. Normalization of blood pressure should not be the only goal in managing the patient with primary aldosteronism. In addition to the kidney and colon, mineralocorticoid receptors are present in the heart, brain, and blood vessels. Excessive secretion of aldos-

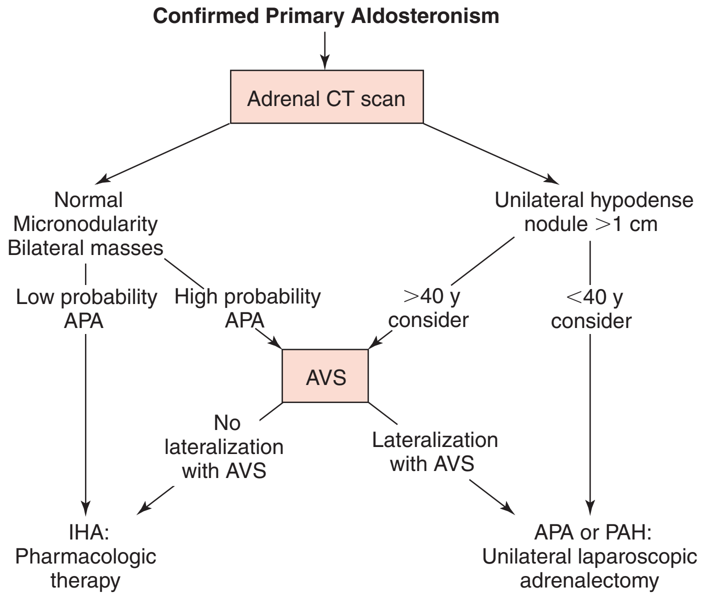

Figure 32–3 Subtype evaluation of primary aldosteronism. See text for details. APA, aldosterone-producing adenoma; AVS, adrenal venous sampling; CT, computed tomography; GRA, glucocorticoid-remediable aldosteronism; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia. (Modified from Young WF Jr, Hogan MJ: Renin-independent hypermineralocorticoidism. Trends Endocrinol Metab 1994;5:97-106.)

terone is associated with increased risk of cardiovascular disease and morbidity. This issue was addressed in a retrospective study that compared 124 patients with primary aldosteronism with 465 patients with apparent essential hypertension who were matched for age, gender, and blood pressure (mean 175/107 mm Hg).[45] The patients with primary aldosteronism had significantly higher rates of stroke (12.9% versus 3.4% in those with essential hypertension), nonfatal myocardial infarction (4.0% versus 0.6%), and atrial fibrillation (7.3% versus 0.6%). The rate of cardiovascular complications appeared to be similar in those with an adrenal adenoma and adrenal hyperplasia.[45] In addition, aldosterone excess can induce adverse cardiovascular effects independently of blood pressure.[46] Therefore, normalization of circulating aldosterone or aldosterone-receptor blockade should be part of the management plan for all patients with primary aldosteronism.

Surgical Treatment of Aldosterone-Producing Adenoma and Unilateral Hyperplasia

Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with APA or unilateral hyperplasia. Blood pressure control improves in nearly 100% of patients postoperatively, and average long-term cure rates of hypertension after unilateral adrenalectomy for APA range from 30% to 60%.[47] Persistent hypertension following adrenalectomy is correlated directly with having more than one first-degree relative with hypertension, use of more than two antihypertensive agents preoperatively, older age, increased serum creatinine, and duration of hypertension and is most likely due to coexistent primary hypertension.[47]

Laparoscopic adrenalectomy is the preferred surgical approach and is associated with shorter hospital stays and less long-term morbidity than the conventional open approach. To decrease the surgical risk, hypokalemia should be corrected with spironolactone preoperatively; treatment with this drug should be discontinued postoperatively. PAC should be measured 1 to 2 days after the operation to confirm a biochemical cure. For the first few weeks postoperatively, serum potassium levels should be monitored weekly and a generous sodium diet should be followed to avoid the hyperkalemia of hypoaldosteronism that may occur because of the chronic suppression of the renin-angiotensin-aldosterone axis. Typically, the hypertension resolves in 1 to 3 months postoperatively. Adrenalectomy for APA has been found to be significantly less expensive than long-term medical therapy.[48]

Pharmacologic Treatment

IHA and GRA should be treated medically.[49] In addition, APA patients may be treated medically if the medical treatment includes mineralocorticoid receptor blockade. A sodium-restricted diet (<100 mEq sodium/d), maintenance of ideal body weight, tobacco avoidance, and regular aerobic exercise contribute significantly to the success of pharmacologic treatment. No placebo-controlled randomized trials have evaluated the relative efficacy of drugs in the treatment of primary aldosteronism.[49] Spironolactone has been the drug of choice to treat primary aldosteronism for more than three decades. Spironolactone is available as 25-, 50-, and 100-mg tablets. The dosage is 12.5 to 25 mg/d initially and increased to 400 mg/d, if necessary, to achieve normokalemia without the aid of oral potassium chloride supplementation. Hypokalemia responds promptly, but hypertension may take as long as 4 to 8 weeks to be corrected. After several months of therapy, the dosage of spironolactone often can be decreased to as little as 25 to 50 mg/d; dosage titration is based on a goal serum potassium level in the high-normal range. Serum potassium and creatinine should be monitored frequently during the first 4 to 6 weeks of therapy (especially in patients with renal insufficiency or diabetes mellitus). Spironolactone increases the half-life of digoxin, and the dosage may need to be adjusted when treatment with spironolactone is started. Concomitant therapy with high-dose salicylates should be avoided because they interfere with the tubular secretion of an active metabolite and decrease the effectiveness of spironolactone. Spironolactone is not selective for the mineralocorticoid receptor, and antagonism at the testosterone receptor and agonism at the progesterone receptor may result in painful gynecomastia, impotence, and menstrual irregularity.[50]

Eplerenone is a newer steroid-based antimineralocorticoid that acts as a competitive and selective mineralocorticoid

receptor antagonist. It was approved by the FDA for the treatment of uncomplicated essential hypertension in late 2003. The 9,11-epoxide group in eplerenone results in a significant reduction of the molecule's progestational and antiandrogenic actions compared with spironolactone; eplerenone has 0.1% of the binding affinity to androgen receptors and <1% of the binding affinity to progesterone receptors compared with spironolactone. Treatment trials comparing the efficacy of eplerenone with spironolactone for the treatment of primary aldosteronism have not been published. Eplerenone will likely be the superior drug if it is shown to be as effective as spironolactone for the treatment of mineralocorticoid-dependent hypertension and if it lacks the limiting antiandrogen side effects of spironolactone.

Patients with IHA frequently require a second antihypertensive agent to achieve good blood pressure control. Hypervolemia is a major reason for resistance to drug therapy, and low doses of a thiazide (e.g., 12.5 to 50 mg of hydrochlorothiazide daily) or a related sulfonamide diuretic are effective in combination with the mineralocorticoid-receptor antagonist. Because these agents often lead to further hypokalemia, serum potassium levels should be monitored.

Pharmacologic Treatment of Glucocorticoid-Remediable Aldosteronism

Before initiating treatment, GRA should be confirmed with genetic testing. Genetic testing should be considered in patients with a family history of primary aldosteronism, onset of primary aldosteronism at a young age (e.g., <20 years old), or a family history of stroke at a young age. In the GRA patient, chronic treatment with physiologic doses of a glucocorticoid normalizes blood pressure and corrects hypokalemia. However, treatment with spironolactone in these patients is just as effective and avoids the potential disruption of the hypothalamic-pituitary-adrenal axis and risk of iatrogenic side effects. A role for glucocorticoid therapy or mineralocorticoid receptor blockade may exist even in normotensive GRA patients.[46]

OTHER FORMS OF MINERALOCORTICOID EXCESS

The spectrum of effects of excess mineralocorticoid in patients with low PRA includes hyperdeoxycorticosteronism, Cushing's syndrome, and apparent mineralocorticoid excess (see Table 32–1). These diagnoses should be considered when PAC and PRA are low in patients with hypertension and hypokalemia (see Fig. 32–2).

Hyperdeoxycorticosteronism

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is caused by enzymatic defects in adrenal steroidogenesis that result in deficient secretion of cortisol. The lack of inhibitory feedback by cortisol on the hypothalamus and pituitary produces an ACTH-driven build-up of cortisol precursors proximal to the enzymatic deficiency. A deficiency of both 11-β-hydroxylase and 17-α-hydroxylase causes hypertension and hypokalemia because of hypersecretion of the mineralocorticoid 11-deoxycorticosterone (DOC). The mineralocorticoid effect of increased circulating levels of DOC also decreases PRA and aldosterone secretion. These defects are autosomal recessive in inheritance and typically are diagnosed in childhood. However, partial enzymatic defects have been shown to cause hypertension in adults.[51]

11-β-Hydroxylase Deficiency

Approximately 5% of all cases of CAH are due to 11-β-hydroxylase deficiency; the prevalence in whites is 1 in 100,000.[52] In addition to high levels of DOC and 11-deoxycortisol, the substrate mass effect results in increased levels of adrenal androgens. Females present in childhood with hypertension, hypokalemia, and virilization, and pseudoprecocious puberty appears in males. Approximately two thirds of patients have mild to moderate hypertension.[53] Markedly increased levels of DOC, 11-deoxycortisol, and adrenal androgens confirm the diagnosis. Glucocorticoid replacement normalizes the steroid abnormalities and hypertension. Glucocorticoid replacement options in adults include dexamethasone (0.5 to 0.75 mg daily), prednisone (5 mg in the morning and 2.5 mg in the evening), or hydrocortisone (20 mg in the morning and 10 mg in the evening). For screening, family members should have the cosyntropin stimulation test for cortisol and 11-deoxycortisol.[52]

17-α-Hydroxylase Deficiency

The 17-α-hydroxylase deficiency form of CAH is rare (only 120 cases have been reported).[54] The deficiency results in decreased production of cortisol and sex hormones. Genetic 46,XY males present with either pseudohermaphroditism or as phenotypic females, and 46,XX females present with primary amenorrhea. Therefore, a person with this form of CAH may not come to medical attention until puberty. The biochemical findings include low concentrations of plasma adrenal androgens, plasma 17-α-hydroxyprogesterone, aldosterone, and cortisol and increased plasma concentrations of DOC, corticosterone, and 18-hydroxycorticosterone, which suppress PRA. As with 11-β-hydroxylase deficiency, glucocorticoid replacement corrects the steroid abnormalities and hypertension. Sex steroids also need to be replaced. For screening, family members should have the cosyntropin stimulation test for cortisol and 17-hydroxypregnenolone.[54]

Deoxycorticosterone-Producing Tumor

DOC-producing adrenal tumors are usually large and malignant.[55,56] Some of them secrete androgens and estrogens in addition to DOC, which may cause virilization in women and feminization in men. A high level of plasma DOC or urinary tetrahydrodeoxycorticosterone and a large adrenal tumor seen on CT confirm the diagnosis. Optimal treatment is complete surgical resection.

Primary Cortisol Resistance

Increased cortisol secretion and plasma cortisol concentrations without evidence of Cushing's syndrome are found in patients with primary cortisol resistance, a rare familial syndrome.[57] The syndrome is characterized by hypokalemic alkalosis, hypertension, increased plasma concentrations of DOC, and increased adrenal androgen secretion, which are probably caused by several defects in glucocorticoid receptors and the steroid-receptor complex. The treatment for the mineralocor-

ticoid-dependent hypertension is blockade of the mineralocorticoid receptor with spironolactone or suppression of ACTH secretion with dexamethasone at the dosages outlined in the preceding sections on primary aldosteronism and CAH, respectively.[58]

Apparent Mineralocorticoid Excess Syndromes

Cortisol can be a potent mineralocorticoid. The microsomal enzyme 11-β-hydroxysteroid dehydrogenase (11-β-OHSD; EC 1.1.1.146) is responsible for the renal metabolism of cortisol to the metabolically inactive cortisone. Deficiency of this enzyme results in a high intrarenal concentration of cortisol, as well as hypertension, hypokalemia, suppressed PRA, and low aldosterone levels.[59,60] An increased ratio of urinary cortisol to cortisone confirms the diagnosis.

Two types of defects have been described in the renal metabolism of cortisol. Type 1 apparent mineralocorticoid excess (AME) syndrome refers to deficiency in the 11-β-OHSD enzyme. Type 2 AME is due to a deficiency in the ring A reduction metabolic pathway.[60] Treatment includes blockade of the mineralocorticoid receptor with spironolactone or suppression of endogenous cortisol secretion with dexamethasone. The congenital forms are rare autosomal recessive disorders.[59] The acquired forms are more common and include licorice-induced hypertension and Cushing's syndrome.

CUSHING'S SYNDROME

Hypertension occurs in 75% to 80% of patients with Cushing's syndrome.[61] The mechanisms of hypertension include increased production of DOC, increased vascular reactivity to catecholamines, and cortisol inactivation overload with stimulation of the mineralocorticoid receptor. Deficient cortisol ring A reduction caused by overload of metabolizing enzymes results in a functional type 2 AME in patients with severe hypercortisolism.[62] Cushing's syndrome is a symptom complex that results from prolonged exposure to supraphysiologic concentrations of glucocorticoids. The source of excess glucocorticoids may be exogenous (iatrogenic) or endogenous. Endogenous Cushing's syndrome is caused by (1) hypersecretion of corticotropin (ACTH), referred to as *ACTH-dependent Cushing's syndrome,* or (2) primary adrenal hypersecretion of glucocorticoids, referred to as *ACTH-independent Cushing's syndrome*. The overall treatment program for patients with Cushing's syndrome includes the resolution of hypercortisolism; the concomitant treatment of the complications of the syndrome (e.g., hypertension, osteoporosis, and diabetes mellitus); and, after definitive treatment, the management of glucocorticoid withdrawal and hypothalamic-pituitary-adrenal (HPA) axis recovery.

Presentation

Typical signs and symptoms of Cushing's syndrome include weight gain with central obesity; facial rounding and plethora; dorsocervical fat pads; easy bruising; fine "cigarette paper" skin; poor wound healing; purple striae; proximal muscle weakness; emotional and cognitive changes (e.g., irritability, crying, depression, restlessness); hypertension; osteoporosis; opportunistic and fungal infections (e.g., mucocutaneous candidiasis, tinea versicolor, pityriasis); altered reproductive function; and hirsutism.

Diagnosis

Accurate diagnosis of Cushing's syndrome and the subtype is essential to direct the appropriate treatment program. Because of the known manifestations of the disorder, hypercortisolism must be suspected and then confirmed with measurements of the serum and 24-hour urine concentrations of cortisol and midnight salivary cortisol. Autonomous hypercortisolism is confirmed with the low-dose dexamethasone suppression test (dexamethasone 0.5 mg orally every 6 hours for 48 hours); a 24-hour urinary cortisol excretion of 20 mcg or greater confirms the diagnosis. The plasma ACTH concentration classifies the subtype of hypercortisolism as either ACTH dependent ("normal" to high levels of ACTH) or ACTH independent (undetectable ACTH).

MRI of the pituitary gland should be performed in patients with ACTH-dependent Cushing's syndrome. If a pituitary tumor is not found with computerized imaging, further evaluation is indicated with imaging of the lungs and inferior petrosal sinus sampling for ACTH with ovine corticotropin-releasing hormone stimulation.

In patients with ACTH-independent hypercortisolism, the high-dose dexamethasone suppression test shows no suppression in urinary cortisol excretion. In these patients, computerized imaging of the adrenal glands usually indicates the type of adrenal disease.

Principles of Treatment

For patients with pituitary-dependent disease, selective pituitary adenomectomy by transsphenoidal surgery is the treatment of choice. The long-term surgical cure rate for ACTH-secreting microadenomas is approximately 90%. If pituitary adenomectomy is not curative, bilateral adrenalectomy and pituitary irradiation are adjunctive treatment options. For patients with primary adrenocortical disease or ectopic ACTH production, surgical extirpation of an adrenal adenoma or carcinoma or the source of ectopic ACTH production is the treatment of choice. For patients with ACTH-independent bilateral macronodular or micronodular hyperplasia, bilateral adrenalectomy is the preferred treatment. Pharmacologic therapy is reserved for patients not cured with these surgical approaches.

The hypertension associated with Cushing's syndrome should be treated until a surgical cure is obtained. Spironolactone, at dosages used to treat primary aldosteronism, is effective in reversing the hypokalemia. Second-step agents (e.g., thiazide diuretics) may be added for optimal control of blood pressure. The hypertension associated with the hypercortisolism usually resolves over several weeks after the surgical cure, and antihypertensive agents can be tapered and withdrawn.

THYROID AND PARATHYROID DISEASE

Dysfunction of the thyroid and parathyroid glands may be the sole cause of hypertension or contribute significantly to underlying primary hypertension.

Thyroid Dysfunction

Presentation and Diagnosis

Hyperthyroidism is the clinical syndrome that occurs when excessive amounts of circulating thyroid hormones interact with thyroid hormone receptors on peripheral tissues. This results in increased metabolic activity and increased sensitivity to circulating catecholamines. Thyrotoxic patients usually have high cardiac output and increased systolic blood pressure.[63]

Hypothyroidism is the syndrome resulting from deficiency of thyroid hormones, which causes many metabolic processes to slow down. The frequency of hypertension, usually diastolic, is increased threefold in hypothyroid patients.[63]

The clinical suspicion of thyroid gland dysfunction is confirmed with laboratory tests. Increased blood levels of thyroid hormones (thyroxine and triiodothyronine) and low serum levels of thyroid-stimulating hormone (TSH) are the hallmarks of hyperthyroidism. The diagnosis of hypothyroidism is based on low serum levels of thyroid hormone and increased serum levels of TSH.

Principles of Treatment

The initial management of patients with hypertension who have hyperthyroidism includes a β-adrenergic blocker (e.g., atenolol) to treat hypertension, tachycardia, and tremor. The definitive treatment of hyperthyroidism is cause specific. For example, patients with autoimmune hyperthyroidism (Graves' disease) should have thyroid gland ablation with ^{131}I. For patients with hyperthyroidism caused by multinodular goiter (Plummer's disease), ^{131}I is usually not curative and subtotal thyroidectomy is the treatment of choice. Finally, if the hyperthyroidism is associated with acute thyroid inflammation (e.g., subacute thyroiditis), only temporary treatment (≈3 months) with a β-adrenergic inhibitor may be necessary.

Treatment of thyroid hormone deficiency decreases blood pressure in most patients with hypertension.[64] Synthetic levothyroxine is the treatment of choice for hypothyroidism. The initial dosage of levothyroxine is based on body weight (1.6 mcg/kg/d). The daily dosage requirement may be lower in older patients (e.g., <1.0 mcg/kg/d). In patients older than 50 years or those with cardiac disease, the initial dosage of levothyroxine should be lower (e.g., a total of 25 to 50 mcg/d) and increased every 2 weeks by 25 mcg until the target dosage is achieved. Clinical and biochemical reevaluations should be completed at 2-month intervals until the serum TSH concentration has normalized.

Primary Hyperparathyroidism

Presentation and Diagnosis

Hypercalcemia is associated with an increased frequency of hypertension. The most common cause of hypercalcemia is primary hyperparathyroidism. The frequency of hypertension in patients with primary hyperparathyroidism varies from 10% to 60%.[65] In most cases the disease is caused by a benign, solitary, parathyroid adenoma. However, when associated with the MEN syndromes, hyperparathyroidism is usually due to hyperplasia of all four parathyroid glands.

Most patients with primary hyperparathyroidism are asymptomatic, and the focus of the presentation may be the side effects of chronic hypercalcemia: polyuria and polydipsia, constipation, osteoporosis, renal lithiasis, peptic ulcer disease, and hypertension.

The hallmarks of primary hyperparathyroidism are hypercalcemia, hypophosphatemia, and an increased serum concentration of parathyroid hormone. In patients with hypercalcemia, measurement of the serum concentration of parathyroid hormone is the most specific way to diagnose primary hyperparathyroidism. If the serum concentration of parathyroid hormone is not increased, the clinical data should be reviewed and nonparathyroid causes of hypercalcemia should be investigated (e.g., pheochromocytoma, hyperthyroidism, cancer, multiple myeloma, vitamin D intoxication, sarcoidosis).

Principles of Treatment

The treatment of hyperparathyroidism is surgical. This involves neck exploration; identification of all four parathyroid glands; and, in sporadic cases, removal of the single adenoma or, in the case of MEN, subtotal (3.5 glands) resection of the hyperplastic glands.

ACROMEGALY

Presentation and Diagnosis

Chronic growth hormone (GH) excess from a GH-producing pituitary tumor results in the clinical syndrome of acromegaly. The effects of chronic excess of GH include acral and soft tissue overgrowth; progressive dental malocclusion; degenerative arthritis related to chondral and synovial tissue overgrowth within joints; low-pitched sonorous voice; excessive sweating and oily skin; perineural hypertrophy leading to nerve entrapment (e.g., carpal tunnel syndrome); cardiac dysfunction; and hypertension. Hypertension occurs in 20% to 40% of the patients.[66-68]

A patient with acromegaly has a characteristic appearance that includes coarsening of facial features, prognathism, frontal bossing, spadelike hands, and wide feet. Often, the patient has a history of progressive increase in shoe, glove, ring, or hat size. These changes may occur slowly and may go unrecognized by the patient, family, and physician.

The diagnosis of acromegaly depends on two criteria: a GH level that is not suppressed to less than 1 mcg/L after an oral glucose load (75 to 100 g) and an increased serum concentration of insulin-like growth factor I. The laboratory assessment of acromegaly is supplemented with MRI of the pituitary.

Principles of Treatment

Treatment is indicated for all patients who have signs and symptoms of acromegaly and biochemical confirmation of the syndrome. The goals of treatment are to prevent the long-term consequences of GH excess, remove the pituitary neoplasm, and preserve normal pituitary tissue and function. Pituitary surgery is the treatment of choice; if necessary, it is supplemented with medical therapy or irradiation, or both.[69,70] The hypertension of acromegaly is most effectively

treated by curing the excess of GH. If a surgical cure is not possible, the hypertension usually responds well to diuretic therapy.

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Chapter 33

Secondary Hypertension: Renal Vascular Causes

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CHAPTER CONTENTS

DEFINITIONS

From a pathologic standpoint, *renovascular hypertension* can simply be defined as elevated blood pressure due to renal hypoperfusion. From the clinical standpoint, it is always a diagnosis confirmed in retrospect. That is, one observes a favorable blood pressure response after successful intervention in a hypertensive patient with suggestive clinical features and a renal artery stenosis suspected of being severe enough to cause hypertension. If blood pressure fails to improve, a patient with essential hypertension and renovascular disease, not renovascular hypertension, is identified. Sorting out renovascular hypertension from essential hypertension with renovascular disease is challenging.

Arteriographic evidence of mild renovascular disease (50% lumen narrowing) was observed in 10.9% of normotensive potential renal transplant donors.[1] However, the prevalence of renovascular disease as a cause of hypertension in the general population is unknown. Estimates are generally in the range of 0.2% to 4%.[2] The presence of significant renovascular disease increases with age. In a population-based study of individuals older than age 65, the prevalence of potentially significant stenosis (>60% lumen narrowing) was 6.8% by duplex ultrasound (more common in men [9.1%] than in women [5.5%]).[3]

Ischemic nephropathy or *azotemic renovascular disease* is a loss of renal function manifested by a reduction in glomerular filtration rate (GFR) or a quantitative loss of renal parenchyma as a consequence of renal artery stenosis affecting the entire functioning renal mass (bilateral renal artery stenosis or stenosis in the renal artery of a solitary functioning kidney).[4] This subset of renovascular disease has unique clinical presentations that occur in the presence or absence of concomitant hypertension.

PATHOPHYSIOLOGY

Renovascular hypertension arises when a lesion impairs blood flow to renal tissue sufficiently to stimulate the renin-angiotensin-aldosterone cascade (Fig. 33–1). Vascular wall stretch receptors sense a reduction in renal perfusion pressure and stimulate juxtaglomerular cells of afferent arterioles to increase renin synthesis and release into the circulation.[5] Renin, a proteolytic enzyme, acts on circulating angiotensinogen formed in the liver to produce the decapeptide, angiotensin I. Angiotensin I is further acted on by the angiotensin-converting enzyme found on endothelial cells throughout the vasculature (especially in the lungs) to produce the octapeptide, angiotensin II. Angiotensin II causes vasoconstriction by a direct effect on vascular smooth muscle cells and by stimulation of the sympathetic nervous system both centrally and peripherally through facilitation of norepinephrine release from sympathetic neurons and catecholamine release from the adrenal medulla.[6] In addition, angiotensin II increases intravascular fluid volume directly by increasing reabsorption of sodium in the proximal renal tubules and indirectly by stimulating aldosterone release from the zona glomerulosa of the adrenal glands, release of antidiuretic hormone from the posterior pituitary gland, and thirst. Thus, hypertension is the consequence of both increased vascular volume and peripheral vascular resistance. Long-term effects of increased angiotensin II include vascular smooth muscle and cardiac hypertrophy.

In unilateral disease the contralateral normal kidney is exposed to increased perfusion pressure, which suppresses its release of renin and increases its excretion of sodium (pressure naturesis). To a limited extent, this dampens the pressor effect of the involved kidney but also produces a chronic stimulus for ongoing renin release. Eventually, chronic exposure to

Figure 33–1 Physiologic and pathologic consequences of renal artery stenosis. SNS, sympathetic nervous system. (Courtesy of the Mayo Clinic.)

increased systemic arterial pressure causes nephrosclerosis in the uninvolved kidney. This may be a cause of persistent hypertension following successful repair of a long-standing renal artery stenosis.

In bilateral disease, initial stimulation of the renin-angiotensin-aldosterone cascade causes an increase in vascular volume. In the absence of an uninvolved kidney, volume expansion persists and may be the dominant mechanism of hypertension. Renin secretion is often suppressed by persistent volume expansion. If vascular volume is lowered, for example by diuretic therapy, the hypertension can be converted back to a renin-dependent form.

ETIOLOGY AND NATURAL HISTORY

Any disorder that impairs perfusion to a kidney enough to stimulate the renin-angiotensin-aldosterone axis can cause renovascular hypertension. Potential causes are listed in Table 33–1. The vast majority of cases are due to atherosclerosis or fibromuscular dysplasia of the main renal arteries or their branches.

Fibromuscular dysplasia is most common in women between the ages of 15 and 50 years.[7] It is a noninflammatory, dysplastic process of the arterial wall leading to renal artery stenosis and impaired renal perfusion. Its cause is unknown, and it is not associated with other cardiovascular risk factors. Fibromuscular dysplasia is bilateral in 35% of cases. It is classified into intimal, medial, and adventitial subtypes on the basis of the layer of the arterial wall that is affected. Medial fibroplasia is the most common subtype and has a characteristic "string-of-beads" appearance on angiography. The beads are typically larger than the diameter of the normal renal segments. Perimedial fibroplasia can present as a focal stenosis or as a "string-of-beads." However, in contrast to medial fibroplasia, the beads are smaller than the normal renal segments. Intimal fibroplasia accounts for <10% of cases and may present as a focal stenosis or as a long, smooth narrowing resembling the lesions seen in large-vessel vasculitis. Adventitial hyperplasia is rare and may present with localized areas of stenosis. Fibromuscular dysplasia typically affects the mid and distal main renal artery segments, often extending into branches. Intimal and adventitial subtypes are more often associated with the complications of dissection and thrombosis. Medial fibroplasia progresses in about 30% of cases but rarely leads to occlusion. Fibromuscular dysplasia accounts for approximately 10% of cases of renovascular hypertension.[8]

Table 33–1 Potential Causes of Renovascular Hypertension

Atherosclerosis
Fibromuscular disease
Renal artery aneurysm
Atheroemboli
Vasculitis:
Takayasu's disease
Polyarteritis nodosa
Arteriovenous malformation
Aortic dissection
Renal artery dissection
Neurofibromatosis-associated renal artery disease
Renal artery trauma
Radiation-induced renal artery stenosis
Surgical ligation of the renal artery
Large intrarenal cysts
Renal artery thrombosis
Subcapsular or perirenal hematoma
Tumor compression
Retroperitoneal fibrosis
Ureteral obstruction
William's syndrome

Atherosclerotic renovascular disease is most common in persons aged 50 years or older who have cardiovascular disease risk factors or manifest atherosclerosis in other vascular beds. Atherosclerotic renovascular disease is bilateral in 30% of cases and has a progression rate of 35% to 50% over a 3- to 5-year period. Progression to occlusion occurs in 3% to 16% over this interval with a greater likelihood in more severely affected vessels at baseline.[8] Atherosclerotic renal vascular disease accounts for a small but increasing proportion of older persons reaching end-stage renal disease.[9-10] It usually affects the proximal renal artery near or at the orifice where it often represents extension of an aortic atherosclerotic plaque across the renal artery orifice.

CLINICAL SYNDROMES

The two major syndromes associated with renovascular disease are renovascular hypertension and ischemic or azotemic nephropathy (Fig. 33–2). Some patients may have manifestations of both syndromes, whereas others may lack signs or

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Figure 33–2 Clinical syndromes associated with renovascular disease. RAAS, renin-angiotensin-aldosterone system; GFR, glomerular filtration rate. (Courtesy of the Mayo Clinic.)

symptoms of either. Unilateral disease is sufficient to cause the syndrome of renovascular hypertension, whereas ischemic nephropathy usually requires bilateral renal artery stenosis or significant stenosis of the renal artery to a solitary functioning kidney. An unknown number of persons with renal artery stenosis do not develop either hypertension or significant abnormalities of renal function. In some but not all cases, this is because the degree of arterial narrowing is insufficient to stimulate the renin-angiotensin-aldosterone axis. Studies suggest that luminal narrowing of >70% to 80% is necessary to stimulate renin secretion.[11] No evidence from prospective studies indicates that revascularization of renal artery stenosis in the absence of associated hypertension or renal dysfunction is of benefit.

Complicating the ability to identify patients with the syndromes of renovascular hypertension or ischemic nephropathy is the recognition that essential hypertension and chronic kidney disease commonly coexist with atherosclerotic renovascular disease. Chronic hypertension interacts with other cardiovascular risk factors to cause generalized atherosclerosis. Increasing evidence suggests that the atherosclerotic process has direct adverse effects on the intrarenal microcirculation leading to renal injury and progressive dysfunction. Aortic atherosclerotic plaques located near the origins of the renal arteries may slowly enlarge over many years and eventually extend across one or both renal artery lumens, causing some degree of stenosis. Older patients with a longstanding history of hypertension present with difficult-to-control blood pressure with or without renal dysfunction and are discovered to have renovascular disease on further evaluation. The majority of these patients will not benefit from revascularization either for blood pressure control or preservation of renal function.

RENOVASCULAR HYPERTENSION

Clinical Clues

Clinical clues suggesting renovascular hypertension are noted in Table 33–2. Essential hypertension usually has its onset in the fourth or fifth decade of life. The onset of hypertension in childhood or young adulthood should always raise suspicion of secondary hypertension. In girls or young women, fibromuscular dysplasia should be considered. The sudden onset or sudden worsening of preexisting hypertension beyond the age of 50 years, especially in a patient who smokes or has other cardiovascular risk factors or who has known coronary, carotid, or aorto-iliac atherosclerosis, should raise suspicion of renovascular hypertension either alone or superimposed on a background of essential hypertension.

Table 33–2 Clinical Clues Suggesting Renovascular Hypertension

History
Onset in childhood, young adulthood or after 50 years of age
Absence of family history of HTN
Short duration (sudden onset)
Recent worsening of preexisting HTN
Symptoms of coronary, cerebral, or peripheral vascular disease
Tobacco use
Diabetes
Accelerated or malignant HTN
Refractory HTN
Examination
Grade III or IV retinopathy
Signs of coronary, cerebral, or peripheral vascular disease (diminished pulses, bruits)
Epigastric abdominal bruit
Laboratory
Hypokalemia
Elevated creatinine
Proteinuria
Dyslipidemia (elevated total/LDL cholesterol, low HDL cholesterol)
Elevated fasting glucose
Small kidney on imaging study

HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein.

Atherosclerosis is a systemic disease. The presence of disease in one vascular bed increases the likelihood of disease in other vascular beds. For example, significant atherosclerotic renovascular disease has been identified in 7% to 39% of patients evaluated for coronary artery disease.[12-17] In these studies, multivariate analyses demonstrated that older age, higher systolic blood pressure, a history of cerebrovascular or peripheral vascular disease, and reduced renal function were independent predictors of the coexistence of renovascular disease. In addition, renovascular disease has been noted in 36% of patients evaluated for peripheral vascular disease and 10% of patients at autopsy who had clinical evidence of stroke.[18,19]

Up to one third of patients who present with the syndrome of accelerated (retinal hemorrhages) or malignant (papilledema) hypertension have an underlying renovascular etiology. Renovascular disease is present in up to 17% of patients with type 2 diabetes mellitus[20] and in 20% of patients with resistant hypertension.[21]

The most specific finding on physical examination is the presence of an epigastric abdominal bruit. Bruits that are high pitched, continuous, or have both systolic and diastolic components suggest significant vascular stenosis. Whereas specificity is high, the sensitivity of an abdominal bruit is low; thus the absence of a bruit on examination is not sufficient to exclude the diagnosis.[22]

Laboratory findings include hypokalemia, a consequence of secondary aldosteronism. An elevated serum creatinine and a urinalysis showing proteinuria are common. Polycythemia due to excess erythropoietin production in response to renal ischemia is a rare finding. A small kidney noted on any imaging study raises suspicion for renovascular disease.

ISCHEMIC NEPHROPATHY

Clinical Clues

Clinical clues suggesting ischemic nephropathy are noted in Table 33–3.[23] Patients with ischemic nephropathy often have hypertension and evidence of extrarenal atherosclerosis.

In the setting of critical bilateral renal artery stenosis or critical stenosis of the renal artery to a solitary kidney, maintenance of transglomerular hydrostatic pressure for filtration depends on angiotensin II–mediated constriction of the efferent arterioles. Specific agents that block angiotensin II generation (angiotensin converting enzyme inhibitors [ACEIs]) or action (angiotensin receptor blockers [ARBs]) result in dilation of efferent artioles associated with an acute and occasionally progressive reduction in GFR.[24] Importantly, in chronic hypertension accompanied by nephrosclerosis, a sudden decrease in blood pressure with any therapy is often associated with a small rise in serum creatinine. This is the consequence of hypertension-related structural changes in the small arteries of the kidney that results in a shift of the renal autoregulatory range of glomerular filtration to a higher minimum blood pressure level. Changes affecting the afferent renal arterioles including endothelial dysfunction with impaired vasodilatation, hyaline arteriosclerosis, and myointimal hyperplasia render them less able to dilate in response to a sudden and significant decrease in blood pressure. This effect on renal function may be greater with drugs that promote dilation of the efferent arterioles. In contrast to changes in renal function due to ischemic nephropathy, increases in serum creatinine are small and usually stabilize or decline with long-term blood pressure control.

Table 33–3 Clinical Clues Suggesting Ischemic Nephropathy

Acute increase in serum creatinine by >20% or progressive increase on repeat testing in response to treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
Acute (flash) pulmonary edema or symptomatic congestive heart failure not explained by cardiac etiologies
Unexplained subacute decline in renal function
Progressive decline in renal function in the presence of known unilateral renal artery disease
Unexplained renal dysfunction or end-stage renal disease

Persons in whom ischemic nephropathy should be considered often demonstrate severe (more than 20%) acute increases in serum creatinine in response to ACEI or ARB therapy or progressive rises in creatinine that do not plateau on serial testing.[24,25] In these situations, the ACEI or ARB should be discontinued and evaluation for ischemic nephropathy considered. The differential diagnosis of acute renal failure complicating ACEI or ARB therapy includes use of these drugs in settings of decreased effective blood volume (concomitant use of high-dose diuretics, severe heart failure), or renal vasoconstriction (concomitant use of nonsteroidal anti-inflammatory drugs, cyclosporine, or tacrolimus).

A spectacular presentation of ischemic nephropathy is the sudden onset of dyspnea from accumulation of fluid in the alveolar spaces of the lungs referred to as “flash pulmonary edema.”[26] Patients usually present in acute respiratory distress of sudden onset and are observed to have significantly elevated blood pressure. Blood pressure reduction with judicious use of diuretics and other medications as needed results in prompt symptomatic relief. Causative factors include underlying hypertensive heart disease with diastolic dysfunction and extracellular volume expansion from renal dysfunction and secondary aldosteronism.[27,28] Acute episodes are often precipitated by labile increases in blood pressure that are common in this disorder. The differential diagnosis of flash pulmonary edema includes cardiac etiologies (acute myocardial infarction, acute aortic or mitral insufficiency) and noncardiac causes (pulmonary embolism and pneumonia). Ischemic nephropathy should also be considered in hypertensive patients who present with congestive heart failure but who do not have ischemic or valvular heart disease.[28]

Ischemic nephropathy should also be considered in all older patients who develop a progressive rise in serum creatinine, especially if there is evidence of extrarenal atherosclerosis and the urinary sediment does not suggest glomerulonephritis.[29] It may be reasonable to consider this disorder in patients with risk factors who present with end-stage renal disease of uncertain cause before initiation of renal replacement therapy. Finally, because atherosclerotic renal vascular disease is a progressive disorder, a rising serum creatinine in a patient with a prior diagnosis of unilateral atherosclerotic renal vascular disease should prompt an evaluation for ischemic nephropathy even if blood pressure is controlled.

The differential diagnosis of a rising creatinine in an older patient with chronic hypertension and extrarenal atherosclerosis includes cholesterol embolization (atheroembolic renal disease), drug-induced interstitial nephritis, and obstructive nephropathy. Although atheroembolic renal disease is often a complication of angiography, vascular surgery, or anticoagulation, it occurs spontaneously in up to 20% of cases.[30] Its association with the development of significant and labile hypertension and a rising serum creatinine frequently raises the suspicion of renovascular disease and ischemic nephropathy. Differentiating atheroembolic renal disease from ischemic nephropathy is important because angiography or vascular interventions can precipitate further cholesterol embolization with dire consequences. Physical findings associated with systemic atheroembolic disease include livedo reticularis and the “blue toe” syndrome. Livedo reticularis consists of a blue-red mottling of the skin in a netlike pattern often visible over the lower extremities and buttocks arising from obstruction of small vessels in the deep dermis. Blue toe syndrome appears as

small, cyanotic, painful lesions on the feet or toes that may ulcerate and often are bilateral. Occasionally, cholesterol emboli are visible on retinal examination. Laboratory findings include anemia, leukocytosis, thrombocytopenia, elevation of the erythrocyte sedimentation rate, serum C-reactive protein, and eosinophilia of the blood and urine.

DIAGNOSTIC EVALUATION

Once renovascular hypertension or ischemic nephropathy is suspected, several noninvasive tests are available to evaluate the status of the renal arteries (Table 33–4). Ideally, screening tests should have sufficient sensitivity and specificity to limit use of invasive angiography (the reference standard for establishing the diagnosis) to those patients with the highest likelihood of having the disorder and benefiting from intervention. Screening tests that approach this requirement are duplex renal ultrasonography, CT angiography, and contrast-enhanced MRA. Screening tests that fail this requirement are intravenous urography, the captopril test, and plasma measurements of peripheral or renal vein renin activity.

INTRAVENOUS UROGRAPHY

This is one of the earliest tests routinely used to screen for renovascular disease. Criteria for a positive test include a difference in length of the kidneys of ≥1.5 cm, delayed appearance of contrast in the caliceal system of the involved kidney, and increased concentration of contrast in the involved kidney on late films. This test is no longer recommended because of poor test characteristics, the limitations of test interpretation and risk of contrast in the presence of azotemia, and the availability of newer and more accurate tests.[31]

PLASMA RENIN ACTIVITY, RENAL VEIN RENIN, AND THE CAPTOPRIL TEST

Although hypertension due to unilateral renal artery stenosis is renin dependent, an elevated plasma renin activity (PRA) is a nonspecific finding that is often observed in essential hypertension.[31] Moreover, PRA is highly variable in patients with renovascular hypertension and low values are frequently observed. Angiotensin II–mediated elevation of blood pressure and salt and water retention returns initially elevated PRA toward normal. In addition, variation in dietary salt intake and many medications influence PRA. All of these factors need to be controlled in order to interpret PRA properly, which makes measuring the PRA level impractical as a screening test. Additionally, in ischemic nephropathy, hypertension is usually volume dependent and associated with low PRA.

Renal vein sampling of PRA is subject to the same limitations just noted and is invasive. However, it may have a limited role in identifying patients with a nonfunctioning kidney due to renal artery occlusion who would benefit from nephrectomy.[32]

The captopril test is carried out by measuring PRA at baseline and repeating the measure 60 minutes after the oral administration of captopril. A significant captopril-induced rise in PRA is consistent with a stimulated renin-axis and increased likelihood of renovascular hypertension. Unfortunately, the effect of captopril on PRA neither significantly increases its sensitivity as a screening test nor eliminates the multiple issues just reviewed that adversely influence its value as a screening test.

CAPTOPRIL RENAL SCINTIGRAPHY

Radionuclide imaging techniques provide information about renal size, perfusion, and excretory function. The test is

Table 33–4 Screening Tests for Renovascular Hypertension

	Test Characteristics		
Test	Sensitivity	Specificity	Comments
Captopril scintigraphy[33, 40]	74% 64-94%	59% 44-98%	Poor sensitivity in presence of renal insufficiency (serum creatinine >1.5 mg/dL), bilateral disease, or disease to a solitary kidney
Duplex renal ultrasound[40]	76% 17-100%	75% 67-98%	Renal insufficiency does not interfere with test performance; does not use contrast; screens for aortic aneurysm and obstructive uropathy; allows estimation of small vessel disease in kidney (resistance index); better than MR angiography for identification of fibromuscular disease
MR angiography[50]	78% 70-87%	88% 86-91%	Renal insufficiency does not interfere with test performance; contrast is non-nephrotoxic; provides images of the aorta, kidneys, and adrenal glands; better than ultrasound for identification of accessory renal arteries and identification of atherosclerotic lesions in obese patients; claustrophobia limits use in some patients
CT angiography[50]	77% 67-86%	94% 92-95%	Provides images of the aorta, kidneys, and adrenal glands; large contrast load limits use in settings of renal insufficiency or contrast allergy: limitations in obese subjects; better than ultrasound for identification of accessory renal arteries; excellent test for identification of renal artery aneurysms and dissection

performed 60 minutes after the oral ingestion of a 50-mg dose of captopril. Radionuclide agents used are radiolabeled pentetic acid (diethylenetriamine pentaacetic acid [DTPA]), a marker of glomerular filtration, or mertiatide (mercaptoacetultriglycine [MAG_3]), a marker of renal blood flow. Renal measurements used to assess for renal artery stenosis include time to maximal radionuclide activity, peak activity, time course of cortical elimination of radionuclide, and estimated single kidney GFR. The rationale for use of captopril is the recognition that in the presence of a critical renal artery stenosis, transcapillary pressure for glomerular filtration depends on angiotensin II–mediated efferent arteriolar constriction. By inducing efferent arteriolar vasodilation, captopril causes an acute decline in GFR and renal blood flow in the affected kidney that is detected by comparing the rates of uptake and excretion of the radionuclide by the individual kidneys. Initial studies performed in highly selected samples in research settings suggested high sensitivity and specificity; however, when studied in clinical practice settings, sensitivity and specificity were similar to those of intravenous urography.[33] Thus, its role in screening for renovascular hypertension is being called into question.

RENAL DUPLEX ULTRASONOGRAPHY

Renal duplex ultrasonography combines B-mode ultrasound with Doppler examination. It is a useful screening test because it provides information about the location and severity of stenosis; provides an estimate of renal size; screens for obstructive uropathy and aortic aneurysm; is safe to perform in the setting of renal insufficiency; is not affected by renal dysfunction; does not require comparisons between the kidneys for interpretation; provides a measure of small vessel disease in the kidneys; and is relatively inexpensive to perform.[31,34] In addition, duplex ultrasonography is the noninvasive test of choice for the follow-up of renal artery stenosis after stent placement. MRA is affected by scatter or artifact produced by the stent. CT angiography can be used but requires contrast and is more expensive than duplex ultrasonography.[35] Diagnosis of renal artery stenosis relies on identification of increases in blood flow velocity at the site of the stenosis. A stenosis of >60% is associated with a peak systolic velocity >200 cm/sec and a renal-to-aortic peak systolic velocity ratio of >3.5.

Measurement of flow velocity in the renal segmental arteries allows calculation of the "resistance index" ([1 – (end-diastolic velocity ÷ maximal systolic velocity]) × 100). Elevation in this measure reflects structural alterations in the small renal arteries associated with nephrosclerosis and identifies patients at increased risk of progressive renal disease.[36] A resistance index >80 may identify patients with renal artery stenosis in whom interventions to relieve the stenosis are less likely to result in blood pressure reduction, improvement in renal function, or long-term kidney survival.[37] However, this may not be highly reliable as an index of poor response to treatment because of a study that showed improvements in blood pressure and renal function in stented patients in whom the resistance index was higher than 80.[38]

Duplex ultrasonography requires significant operator skill, it may miss accessory renal arteries (sensitivity ≈67%) or stenosis in the distal main renal artery or branches, and it is technically unsatisfactory in 4% to 13% of cases due to obesity or the presence of excessive bowel gas.[31]

COMPUTED TOMOGRAPHIC ANGIOGRAPHY

CT angiography provides images of the renal arteries and aorta. This study also provides an estimate of renal size and imaging of renal and adrenal morphology.[39] CT angiography consists of an initial noncontrast CT image of the abdomen followed by CT angiography. Axial images are obtained during a breath hold timed to coincide with the arterial phase of a bolus infusion of contrast into a peripheral vein. The acquired data are then reformatted using several different software programs to obtain 2- and 3-D reconstructed images. Operator experience, equipment, and variation in the reformatting technique used can influence test performance. Overall sensitivity and specificity are higher than for duplex ultrasound.[40] However, a relatively large amount of contrast is required (120 to 150 mL), limiting its use in the setting of renal insufficiency or contrast allergy; it uses ionizing radiation; and it is more expensive than duplex ultrasonography. Similar to duplex ultrasonography, this study is less useful in obese patients due to limitations of table movement for image acquisition. Patients must be able to suspend respiration during image acquisition because respiratory artifact can significantly degrade image quality. Atherosclerotic disease is identified more readily than fibromuscular disease. CT angiography is a good test to identify renal artery dissection and aneurysms and is better than duplex ultrasound for identification of accessory renal arteries.

CONTRAST-ENHANCED MAGNETIC RESONANCE ANGIOGRAPHY

Similar to CT angiography, contrast-enhanced MR angiography provides images of the renal arteries, aorta, kidneys, and adrenal glands.[41] The test begins with routine T1- and T2-weighted images for evaluation of the abdominal organs including the kidneys and adrenal glands. Subsequently, data are acquired during a breath hold timed to coincide with the arterial phase of a bolus infusion of gadolinium from an antecubital vein. Similar to CT angiography, software programs are then used to construct 3-D multiplane reformations. Although MR angiography itself is operator independent, considerable expertise is required for processing and interpretation of the images. In addition, patients must be able to suspend breathing during data acquisition because respiration can induce significant artifact. Unlike CT angiography, this test can be performed safely in the setting of renal insufficiency or contrast allergy. Contrast-enhanced MR angiography is better than duplex ultrasonography in identifying accessory renal arteries and does not require exposure to ionizing radiation. Overall, sensitivity and specificity are similar to those of CT angiography.[40] Contrast-enhanced MR angiography is superior to duplex ultrasonography for the identification of atherosclerotic lesions, especially in obese subjects.[42,43] However, it is more expensive and has reduced sensitivity for the identification of fibromuscular dysplasia, which is better identified by duplex ultrasonography. In up to

one third of patients the severity of the stenosis may be overestimated.[44] Not all patients can be examined with MR imaging. Claustrophobia is a limitation that often can be overcome with the use of sedatives. Patients with metallic implants, such as mechanical heart valves and cerebral aneurysm clips, or electrically activated implants, such as pacemakers, cannot be studied.

CONTRAST ANGIOGRAPHY

Contrast angiography remains the reference standard. Percutaneous intervention with or without stenting can be carried out at the time of diagnostic angiography if an amenable lesion is identified. A major advantage of contrast angiography is superior spatial resolution allowing for clear visualization of all portions of the renal artery including branches and identification of accessory renal arteries. However, a limitation of angiography is the restricted number of planes of projection that may cause underestimation of the severity of eccentric stenoses and make it difficult to identify the origins of the renal arteries in the presence of a tortuous aorta. In addition, risks of contrast angiography include access site complications of hematoma, pseudoaneurysm, and arterial venous fistula, contrast-induced allergy and acute renal failure, and atheroemboli.

Contrast-induced acute renal failure is associated with increased morbidity and mortality. It is uncommon in patients with normal renal function. Risk factors in the setting of impaired renal function include high doses of ionic, hyperosmolar contrast agents; diabetes; congestive heart failure; volume depletion; and concomitant use of potentially nephrotoxic drugs.[45,46] A number of methods have been studied to reduce the risk of contrast-induced acute renal failure. Hydration with 0.9% saline is helpful. In addition, use of smaller doses of nonionic, low osmolar agents is beneficial. Hydration with a sodium bicarbonate solution has also been shown to be promising.[49] Finally, the use of noniodinated contrast agents, such as CO_2 and gadolinium, should be considered in the setting of significant renal dysfunction (GFR <30 mL/min or serum creatinine >2.0 mg/dL).

APPROACH TO THE DIAGNOSTIC EVALUATION

Figure 33–3 depicts an approach to the diagnostic evaluation for identification of renovascular disease. A number of caveats regarding screening tests for renovascular disease should be kept in mind.

First, estimates of the test characteristics of the available noninvasive screening tests vary widely (see Table 33–4). This may be due to several factors including variation in expertise of test performance and interpretation, publication bias, and sample selection. A meta-analysis of diagnostic tests for renal artery stenosis demonstrated superior diagnostic accuracy of duplex ultrasonography, CT angiography, and contrast-enhanced MRA over captopril scintigraphy.[43] Thus, these three tests should be considered as the preferred noninvasive screening tests for identification of renal artery stenosis. Overall, diagnostic accuracy of CT angiography and contrast-enhanced MRA appears to be superior to duplex ultrasonography; however, cost, local availability and expertise, and patient-specific factors are important considerations for specific test selection.

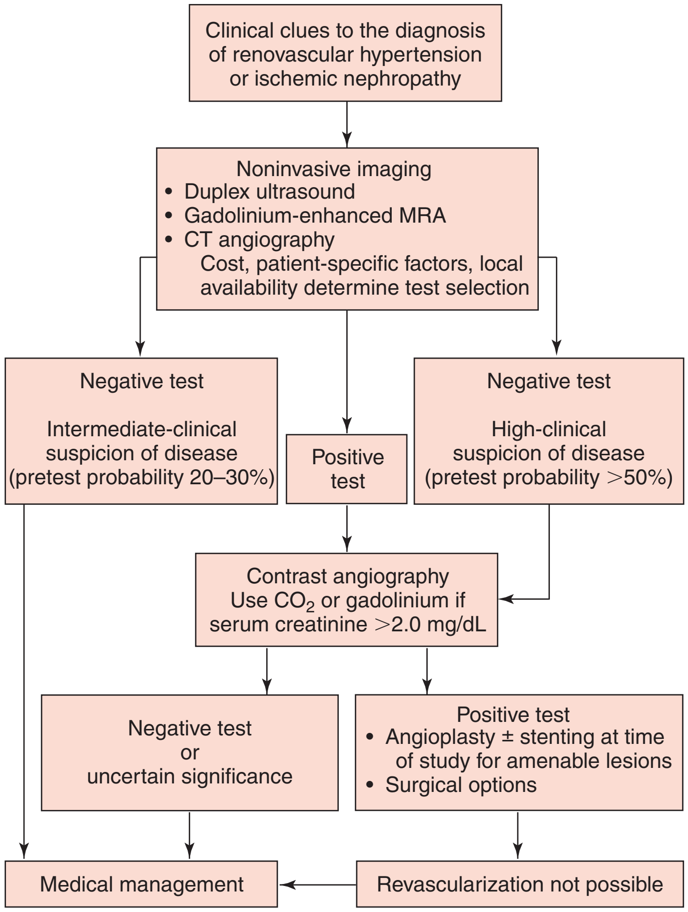

Figure 33–3 Diagnostic approach for renovascular hypertension. CT, computed tomography; MRA, magnetic resonance angiography.

Second, the noninvasive tests are better for identification of atherosclerotic disease than for fibromuscular dysplasia. Overall, duplex ultrasound is probably the best choice to screen for fibromuscular disease. In patients with a high probability of fibromuscular disease, contrast angiography should be considered if the results of noninvasive screening are ambiguous.

Third, a multicenter, prospective comparative study of CT angiography and contrast-enhanced MRA demonstrated that both studies had sensitivities below 90% for detection of significant atherosclerotic renal artery disease.[50] Thus, given our current understanding of the diagnostic accuracy of noninvasive tests, their primary value appears to be in the evaluation of patients with an intermediate pretest probability of disease (20% to 30%). This is the most commonly encountered circumstance in clinical practice. In this setting a technically satisfactory noninvasive screening test that is negative reduces the post-test probability of disease to <5%, a probability that does not justify further evaluation (see Chapter 1). On the other hand, if the pretest probability is >50%, a negative screening test still results in a significant residual (post-test) probability of disease, often >20%, a level that may justify further evaluation. Thus, in the setting of a high pretest

probability of disease, contrast angiography should be considered either as the initial test in patients at low risk of complications from the study or as a subsequent study if the results of noninvasive screening tests are ambiguous. Clinical prediction rules to estimate the pretest probability of renovascular disease are available.[51,52]

MANAGEMENT OF RENOVASCULAR DISEASE

The major treatment goals are to reduce morbidity and mortality by lowering blood pressure and improving or stabilizing renal function. Treatment options include several revascularization procedures consisting of various surgical options or angioplasty with or without endovascular stenting or conservative medical management. Because "cure" of hypertension is often not achieved, most patients with renovascular disease and hypertension require lifelong medical management regardless of the use of revascularization therapies. In addition to blood pressure control, medical management includes identification and treatment of all modifiable cardiovascular risk factors because the most common causes of morbidity and mortality in hypertensive patients with renovascular disease are coronary artery disease and stroke.

MEDICAL THERAPY

Because renovascular disease is a potentially curable form of hypertension, the first consideration should be for revascularization. However, there are several settings in which medical therapy without concomitant revascularization is a reasonable option (Table 33–5). Medical therapy is appropriate if the hemodynamic significance of a renal artery lesion is questionable, if it is not amenable to revascularization because of its location (lesions in segmental arteries or involving branch points), or if the patient declines interventional therapy. Many older patients with long-standing hypertension and chronic, stable renal insufficiency are discovered to have renovascular disease. As noted earlier, the majority of these patients have essential hypertension and should be treated medically. Medical therapy is also preferred if the renal artery lesion is hemodynamically significant but there is evidence of advanced ischemic injury to the affected kidney manifest by renal atrophy (cortical thinning, renal length <8 cm) or a high resistance index by ultrasonography (>80).[37] In addition, medical therapy is the appropriate option for most patients with a significant elevation of serum creatinine and associated markers of parenchymal renal disease because the risk of renal failure associated with invasive therapies is high and the favorable outcomes of lower blood pressure and improved renal function are rarely observed. This would include patients with unilateral disease and a serum creatinine >2.5 mg/dL or patients with bilateral disease and a serum creatinine >3.0 mg/dL, especially in the presence of markers of parenchymal renal disease (cortical atrophy, small kidneys, high resistance index). Lastly, the medical option may be chosen if atherosclerotic renovascular disease is present in a patient who is at high risk for surgery and who has a severely diseased aorta with ulcerative plaques, for which the risk of atheroembolism from catheter based intervention is increased.

Table 33–5 Indications for Medical Treatment of Renovascular Hypertension

Uncertain hemodynamic significance of the renal artery lesion
Renal artery stenosis not amenable to revascularization
Patient declines revascularization
Chronic stable hypertension and renal dysfunction
Evidence of advanced ischemic injury to the stenotic kidney
Advanced renal insufficiency
Unilateral renal artery stenosis with a serum creatinine >2.5 mg/dL
Bilateral renal artery stenosis with a serum creatinine >3.0 mg/dL
Renal artery stenosis and a severely diseased aorta

The goal of drug therapy should be to lower office blood pressure to <140/90 mm Hg. In the presence of concomitant diabetes mellitus or chronic kidney disease, a lower goal of <130/80 mm Hg should be achieved.[53] Pharmacologic treatment should be focused on blocking angiotensin II production or the angiotensin II receptor, or both, and the postreceptor effects of angiotensin II, as well as lowering blood pressure to goal. Importantly, most patients with renovascular disease have resistant hypertension and require antihypertensive drugs in addition to those that block the renin-angiotensin-aldosterone system (RAAS). Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be considered as initial drugs of choice. The availability and widespread use of these drugs are largely responsible for improved blood pressure control rates in patients with renovascular disease.[54] Because these drugs only partially inhibit the production of angiotensin II or interaction of angiotensin II with its receptor, titration to maximum-tolerated doses is often beneficial. Moreover, dual blockade of the renin-angiotensin cascade by using combination therapy with both an ACEI and an ARB can be more effective than either agent used alone. This option can be considered in cases of resistant hypertension if other strategies have failed.[55] When these classes of drugs are used, serum creatinine and potassium should be measured within 1 week of initiation of therapy and with subsequent dose increases.

Angiotensin II stimulates production and release of aldosterone from the zona glomerulosa of the adrenal glands leading to salt and water retention, which contributes to blood pressure elevation in patients with renovascular disease. Moreover, reduction in aldosterone levels observed acutely with ACEI or ARB therapy often becomes less evident with chronic therapy.[56] This phenomenon of "aldosterone escape" may be due to an increase in angiotensin II formation from alternative non-ACE pathways interacting with a reactive increase in the number of angiotensin II receptors. In addition, hyperkalemia from ACEI or ARB therapy stimulates aldosterone production. Thus, diuretic therapy is highly effective in combination with ACEI or ARB therapy for blood pressure control in the majority of patients with renovascular hypertension. In cases of resistant hypertension, the use of specific mineralocorticol receptor antagonists can also be considered, especially if aldosterone is observed to be elevated; however, if these agents are used in combination with an ACEI or ARB, potassium must be carefully monitored.

Multiple other antihypertensive drugs are potentially useful. Renovascular hypertension is characterized hemodynamically by increased peripheral vascular resistance; thus direct vasodilators are useful. These include the calcium channel blockers, hydralazine, and minoxidil. When used alone, hydralazine and minoxidil cause reactive fluid retention and sympathetic nervous system stimulation, so they should be used only in combination with a diuretic and an adrenergic inhibitor. β-Blockers are also useful in part because of their ability to inhibit sympathetically mediated renin release. Finally, because angiotensin II stimulates sympathetic nervous system activity, sympatholytic drugs, such as clonidine or guanfacine, can be considered. However, because of their side-effect profiles, these drugs are generally used selectively in patients who are not controlled with standard therapies.

In all patients with renovascular hypertension and especially in those with atherosclerotic disease, medical management should also include therapies to inhibit progression of atherosclerosis. Treatments include smoking cessation strategies, platelet inhibition, and the use of pharmacologic therapies for lipid control. Therapy with statins may retard progression or even induce regression of atherosclerotic renal vascular lesions.[57]

Blood pressure reduction without revascularization can aggravate ischemic injury to an affected kidney. In addition, progression of a lesion to occlusion or renal artery thrombosis with irreversible loss of the affected kidney can occur. These adverse outcomes are rare with fibromuscular disease and primarily occur in atherosclerosis. In unilateral disease, these adverse events are not always associated with a rise in serum creatinine. In bilateral disease or in unilateral disease in the presence of nephrosclerosis, a small rise in creatinine with acute blood pressure reduction is common, especially following initiation of therapy with an ACEI or ARB.[24] In some cases this is due to the acute loss of angiotensin II–dependent efferent arteriolar vasoconstriction, which is needed to maintain adequate transcapillary glomerular pressure for filtration. In other cases, it is simply due to reduction in systemic blood pressure below the level of autoregulation of glomerular filtration in kidneys harboring changes of nephrosclerosis from chronic hypertension. With continued therapy, creatinine stabilizes and may decline. However, in 2% to 6% of cases, a large increase in creatinine may occur acutely following initiation of treatment with an ACEI, ARB, or diuretic.[58] This change can be quickly reversed by reducing or discontinuing diuretic, ACEI, or ARB therapy. Following recovery of renal function, revascularization should be considered in patients with bilateral disease.

Overall, the development of progressive renal failure is uncommon in most patients with atherosclerotic disease managed medically.[59-61] Nevertheless, this potential adverse outcome should be discussed with the patient at the onset of medical therapy. Serial measures of renal function and size are important components of follow-up care. A rising serum creatinine should trigger a diagnostic evaluation that includes evaluation for progressive renal artery occlusive disease and the possible need for revascularization.

REVASCULARIZATION

Although it is uncertain whether revascularization strategies are superior to medical treatment in most patients with renovascular disease and hypertension or renal dysfunction, it is reasonable to consider some subgroups for interventional therapy (Table 33–6). In general, patients with recent onset hypertension (<5 years' duration) or those with chronic hypertension who experience an unambiguous acute increase in blood pressure are more likely to have a favorable outcome from revascularization than are patients with chronic stable hypertension.[8] In addition, patients who have a good blood pressure response to an ACEI or ARB are likely to have a similar response to successful revascularization, although the opposite is not always true. In younger patients, who are at lower risk of complications, elimination of or reduction in the need for antihypertensive medications is an appropriate indication for choosing revascularization. This group includes most patients with fibromuscular dysplasia and some patients with atherosclerotic renal disease. Whether revascularization results in lower rates of morbidity, mortality, or end-stage renal disease than medical management and good blood pressure control in the long term remains uncertain.

Generally, patients with refractory hypertension have benefited from revascularization with lower blood pressure and a reduced medication requirement.[62] Refractory hypertension is defined as blood pressure above goal despite the use of full doses of three antihypertensive drugs including a diuretic. Some patients have refractory hypertension because of intolerance to medication or poor compliance with long-term treatment. They should also be considered for revascularization.

In current practice, preservation of renal function is a more common indication for revascularization than blood pressure control. This indication occurs almost exclusively in patients with atherosclerotic renal artery disease. They are usually older and have evidence of systemic atherosclerosis. Identifying patients who are most likely to experience improvement or stabilization of renal function from revascularization

Table 33–6 Indications for Renal Revascularization

Fibromuscular dysplasia
Atherosclerosis:
Younger patients (<70 yr old) with recent onset or worsening of hypertension
Refractory hypertension
Full doses of 3 drugs, including a diuretic appropriate for level of renal function
Hypertension-dependent renal function
Compelling indication for ACEI or ARB therapy + ACEI or ARB-induced acute renal failure
Flash pulmonary edema
Refractory congestive heart failure with bilateral renal artery stenosis
Recent and progressive decline in renal function:
Critical stenoses that are bilateral or stenosis in a solitary functioning kidney
Renal size >8 cm, resistance index <80, serum creatinine <3.0 mg/dL
Other causes of renal dysfunction excluded (obstruction, interstitial nephritis, atheroembolic renal disease, glomerular disease)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

is challenging. For patients with a recent and progressive rise in creatinine that is unexplained and who have markers of "salvageable" kidneys based on adequate renal size, cortical thickness and normal resistance indices are most likely to benefit from revascularization procedures. Studies to date have shown that revascularization procedures in patients with renal insufficiency are associated with improved renal function in approximately 25% of cases and no acute change but long-term stabilization of renal function in approximately 50%. Of concern is the observation that in approximately 25% of patients, renal function continues to deteriorate, sometimes in an accelerated fashion, following a revascularization procedure.[63] The factors that cause acute deterioration in renal function are not well understood but include renal atheroembolization and contrast toxicity. Given the potential for worsening of renal function with intervention, patients with stable chronic renal insufficiency and controlled blood pressure should probably not be considered for revascularization. With rare exception (subacute decline in renal function with normal-sized kidneys), patients with advanced renal insufficiency (serum creatinine >3.0 mg/dL) do not benefit from revascularization.

As noted previously, in some patients with bilateral renal artery stenosis, lowering of systemic pressure with any drug combination reduces renal perfusion pressure below the autoregulatory range, causing an acute and progressive decline in renal function. In such patients, adequate control of blood pressure and stable renal function cannot be achieved and revascularization should be considered. In patients who demonstrate acute renal failure with ACEI or ARB therapy and in whom a compelling indication for use of these drugs exists, revascularization may be reasonable.

Lastly, bilateral atherosclerotic renal artery stenosis can be an important precipitating cause of recurrent episodes of flash pulmonary edema and congestive heart failure. Revascularization has been shown to be effective in reducing the frequency of such events in association with significant decreases in blood pressure.[64]

PERCUTANEOUS INTERVENTION

Percutaneous angioplasty is the treatment of choice for amenable lesions due to fibromuscular dysplasia. The major indication is hypertension because this disease rarely progresses to total occlusion with loss of renal function. The majority of patients are young and have normal renal function; thus the risks of intervention are minimal. Technical success rates are >90%. Cure rates of hypertension range from 14% to 59%, and improvement rates range from 21% to 59%. Failure rates range from 2% to 30%.[7] Restenosis rates are <10%. Stenting is rarely required but is used if angioplasty results are inadequate or if renal artery dissection occurs.

Stent-supported angioplasty has supplanted surgery in most centers for the treatment of atherosclerotic renal artery stenosis. Stenting is required for ostial lesions. Compared with angioplasty alone, stent-supported angioplasty is associated with a higher technical success rate and a lower restenosis rate in follow-up.[65] Currently, restenosis at 1 year occurs in approximately 26% of patients treated with angioplasty alone compared with 17% treated with stent-supported angioplasty.

Complications of percutaneous intervention occur in 7% to 11% of cases. The most frequent complication is groin hematoma. More severe complications include renal failure, segmental renal infarction, renal artery rupture, dissection or thrombosis, and atheroembolization. The use of distal protection devices to trap embolic debris may lessen the latter complication, but this needs further study.

SURGERY

Surgical revascularization is largely reserved for patients who have lesions that are not amenable to percutaneous intervention or in whom percutaneous therapy has failed. In addition, surgery is the treatment of choice when concomitant replacement of the aorta (aneurysm or severe aorto-iliac disease) is required. Long-term results of surgery on blood pressure and renal function have been favorable.[66] In patients with minimal aortic disease, aorto-renal bypass using an autogenous segment of the saphenous vein or hypogastric artery is commonly performed. A synthetic graft can be placed if an autogenous graft is not available. Renal artery endarterectomy is also commonly performed. In older patients with severe atherosclerosis of the abdominal aorta, hepato-renal bypass on the right and spleno-renal bypass on the left can be performed. Such interventions require a patent celiac artery. Additionally, in these patients, renal artery bypass to the supra-celiac or lower thoracic aorta can be considered. Operative mortality ranges from 2% to 8% and is higher in patients who require aortic replacement. The most common causes of death are myocardial infarction and stroke. Evaluation for and correction of significant coronary or carotid disease before renal revascularization is advocated by some experts, but the impact on operative mortality has not been formally assessed. Lastly, nephrectomy can be considered for atrophic kidneys due to renal artery occlusion. Lateralization of renal vein renin levels to the affected kidney predicts an increased likelihood of lower blood pressure with surgery.[32] Laparoscopic techniques have lessened the morbidity associated with this procedure.

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Chapter 34

Treatment of Hypertension in the Patient with Cardiovascular Disease

George Chrysant and Suzanne Oparil

CHAPTER CONTENTS

Approximately 70 million Americans have CVD including 65 million with HTN, 13 million with CHD, 5.5 million with stroke, 1 million with congenital heart disease, and 5 million with HF (Fig. 34–1).[1,2] HTN both accelerates the progression of atherosclerotic disease and leads to LVH, resulting in diminished coronary reserve and exacerbating the ischemic effects of obstructive CHD. Approximately 50% of CHD events and 65% to 70% of strokes are due to suboptimal control of blood pressure.[3]

The risk of CVD in the patient with HTN can be greatly reduced with effective antihypertensive therapy, and the major reductions in CVD morbidity and mortality over the past 50 years have been attributed, in part, to the increased availability and utilization of antihypertensive therapy.[4] The use of antihypertensive drugs has greatly increased in the past 50 years. For example, in the Framingham Heart Study cohort, antihypertensive drug use increased from 2.3% to 24.6% in men and from 5.7% to 27.7% in women over this period. This correlated with a decline in the prevalence of high BP, particularly severe HTN (SBP > 160 mm Hg or DBP > 100 mm Hg) from 18.5% to 9.2% in men and 28% to 7.7% in women, as well as a reduction in the prevalence of LVH over the same period. Reductions of 4 to 8 mm Hg in mean BP reduce the risk of stroke and CHD by 28% to 38% and 20% to 22%, respectively.[5]

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndromes; AF, atrial fibrillation; MI, myocardial infarction; ARB, angiotensin II type 1 receptor blocker; BB, beta-adrenergic receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; CHD, coronary heart disease; DM, diabetes mellitus; DBP, diastolic blood pressure; ESRD, end-stage renal disease; HF, heart failure; HTN, hypertension; ISH, isolated systolic hypertension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; PP, pulse pressure; PAD, peripheral arterial disease; PWV, pressure wave velocity; RAAS, renin-angiotensin-aldosterone system; RWT, relative wall thickness; SBP, systolic blood pressure; U.S., United States.

In a meta-analysis of 61 studies of 1 million adults with no previous vascular disease recorded at baseline, BP was directly related to fatal CHD, fatal stroke, and overall mortality over the entire range down to a BP of 115/75 mm Hg.[6] For persons 40 to 69 years of age, each reduction in SBP of 20 mm Hg (or 10 mm Hg in DBP) reduced the relative risk of fatal stroke (hazard ratio 0.36 to 0.43), fatal CHD (0.49 to 0.54), and death by more than half (Fig. 34–2A and B). Absolute risk of these outcomes increases greatly with age, such that for any given SBP the absolute risk of fatal stroke or CHD is increased more than 15-fold for persons aged 80- to 89-years-old compared with those aged 50- to 59-years-old. Accordingly, for any given reduction in SBP, the reduction in absolute risk of fatal stroke or CHD is more than 15-fold greater in the older than in the younger age groups, supporting the concept that treating hypertension in the elderly is highly beneficial.

The risk of CVD morbidity and mortality in persons with HTN is also influenced by concomitant CVD risk factors, target organ damage, or established CVD. A 25-year observational study of men from different parts of the world (U.S., Japan, Serbia, Northern Europe, Mediterranean southern Europe, inland southern Europe) showed that, although the relative increase in mortality from CHD for a given increase in BP did not differ significantly among the six groups, the absolute age-adjusted mortality risk from CHD at the same level of BP elevation varied by a factor of > 3 among populations.[7] These findings highlight the importance of assessing total CVD risk when considering treatment options for persons with HTN (Table 34–1).[8] Hypertensive persons with established CVD, diabetes, or renal insufficiency are at the highest risk for CVD morbidity and mortality and deserve the most aggressive treatment. This chapter discusses the assessment and therapy of hypertensive persons with concomitant CVD. Treatment considerations for diabetics and persons with renal insufficiency are discussed in Chapter 35.

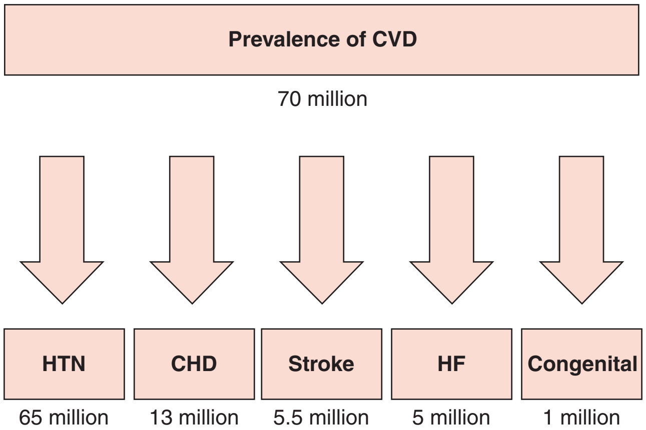


Figure 34–1 The prevalence of hypertension, coronary heart disease, stroke, congenital heart disease, and heart failure in the United States. From NHLBI Morbidity and Mortality Chart Book, 2005. (Reproduced with modification from Morbidity and Mortality: 2005 Chartbook on Cardiovascular, Lung and Blood Diseases. National Institute of Health. National Heart, Lung and Blood Institute).

SYSTOLIC BLOOD PRESSURE, ISOLATED SYSTOLIC HYPERTENSION, PULSE PRESSURE, AND CARDIOVASCULAR DISEASE RISK

SBP is a more robust predictor of HTN-related morbidity and mortality than is DBP in persons 50 years or older, in whom it represents a form of target organ damage resulting from prolonged BP elevation. Further, randomized controlled outcomes trials of antihypertensive treatment have demonstrated a robust linear relationship between treatment-related reduction in SBP and risk for a variety of outcomes including stroke, CHD, CVD death, total mortality, and major CVD events, independent of drug class administered.[5] Accordingly, current hypertension treatment guidelines recommend targeting SBP rather than DBP in managing the older hypertensive patient.[8] In persons who have elevated or high normal BP at an early age, the increased wall tension leads to thinning, fragmenting, and fracture of elastin fibers, as well as increased collagen deposition in the central arteries, resulting in progressive stiffening and decreased compliance of these vessels. In addition to these structural abnormalities, endothelial dysfunction, which develops over time as a consequence of both aging and HTN, contributes functionally to increased arterial rigidity in elderly persons with a widened PP and subsequent ISH.[9-12] Reduced nitric oxide (NO) synthesis or release in this setting, or both, results in diminished endothelium-dependent vasodilation of forearm vessels and contributes to increased wall thickness of conductance vessels, such as the common carotid artery.[13]

Isolated elevation of SBP is common with increasing age because SBP rises continuously until the eighth or ninth decade of life, while DBP levels off or declines after the sixth decade.[12,14] In older individuals, the diagnosis of HTN is more often made on the basis of SBP than DBP. The combination of increased SBP and decreased DBP creates a widened PP and contributes to the increased prevalence of ISH with advancing age. ISH (BP > 160/ < 90 mm Hg) occurs in 15% of men and women aged 60 years or older and in more than 20% of those aged 80 years and older.[14] As PP widens, it begins to correlate closely with SBP due to increased arterial stiffness and decreased compliance.[12] PP has been linked to advanced atherosclerotic disease and CVD events, such as fatal and nonfatal MI and stroke, and is a better predictor of CVD risk than SBP or DBP alone.

Compliance is defined as "the relationship between changes in distending pressure (ΔP) inside the artery and concomitant changes in radius [or in volume (ΔV)]," and is represented by the slope of $\Delta V/\Delta P$. As arterial stiffness increases, a higher distending pressure is required for a given change in the radius of the artery.[15] Increasing arterial stiffness, as indexed by PWV, contributes to a greater PP. A pressure wave is generated with each ejection of blood from the LV. The pressure wave moves away from the heart at a finite speed that is dependent on compliance. The wave is reflected at any point of discontinuity in the arterial tree, and the reflected wave returns to the aorta and LV. In younger persons, the PWV averages 5 m/s. At this speed, the reflected wave usually reaches the aortic valve after closure, leading to a higher DBP and enhancing coronary perfusion by providing a "boosting" effect. As persons age and central arterial compliance decreases, PWV can reach 20 m/sec. At this speed the reflective wave reaches the aortic valve before closure, leading to both a higher SBP and afterload and a decreased DBP, in some cases compromising coronary perfusion pressure.[16] Other factors, such as a slow heart rate, can also affect PWV and augmentation of central aortic systolic pressure. Augmentation of central aortic systolic pressure, as seen in aging and in the presence of hypertension or arterial disease, or both, greatly increases cardiac work and pressure-related cardiac pathology because it is the pressure against which the LV must eject blood into the systemic circulation.[17]

Direct measurement of central aortic pressure is not practical in a clinical setting because it requires invasive arterial catheterization. Instead, central aortic pressure waveforms are derived from peripheral (radial) artery pressure waveforms recorded directly by applanation tonometry using a validated generalized transfer function.[18-21] Computerized analysis is used to delineate first (outgoing) and second (reflected) pressure wave components (T1, T2) during systole (Fig. 34–3). The pressure at the peak of the outgoing pressure wave is identified as P1, and the pressure difference between this point and the maximal pressure during systole (ΔP, or augmentation) is identified as the reflected pressure wave occurring during systole. Augmentation index is defined as the ratio of augmentation to central pulse pressure and is expressed as a percentage ($A|x = (\Delta P/PP) \times 100$). Pulse pressure amplification is expressed as the ratio of central pulse pressure (CPP) to peripheral (brachial) pulse pressure (PPP) (PP amplification = PPP/CPP). This methodology, although technically challenging, is being applied in the research setting to mechanistic and outcome studies of antihypertensive therapies.

The measurement of PWV involves recording the time interval of the pulse between two points, which are usually the carotid artery and the femoral artery using two pressure transducers and the distance traveled (PWV [m/sec] = distance [m]/transit time [sec]). This can be achieved using two methods. The first is to manually record the time interval between the carotid and femoral arteries over the course of 10 heart beats followed by correcting for the paper speed (time

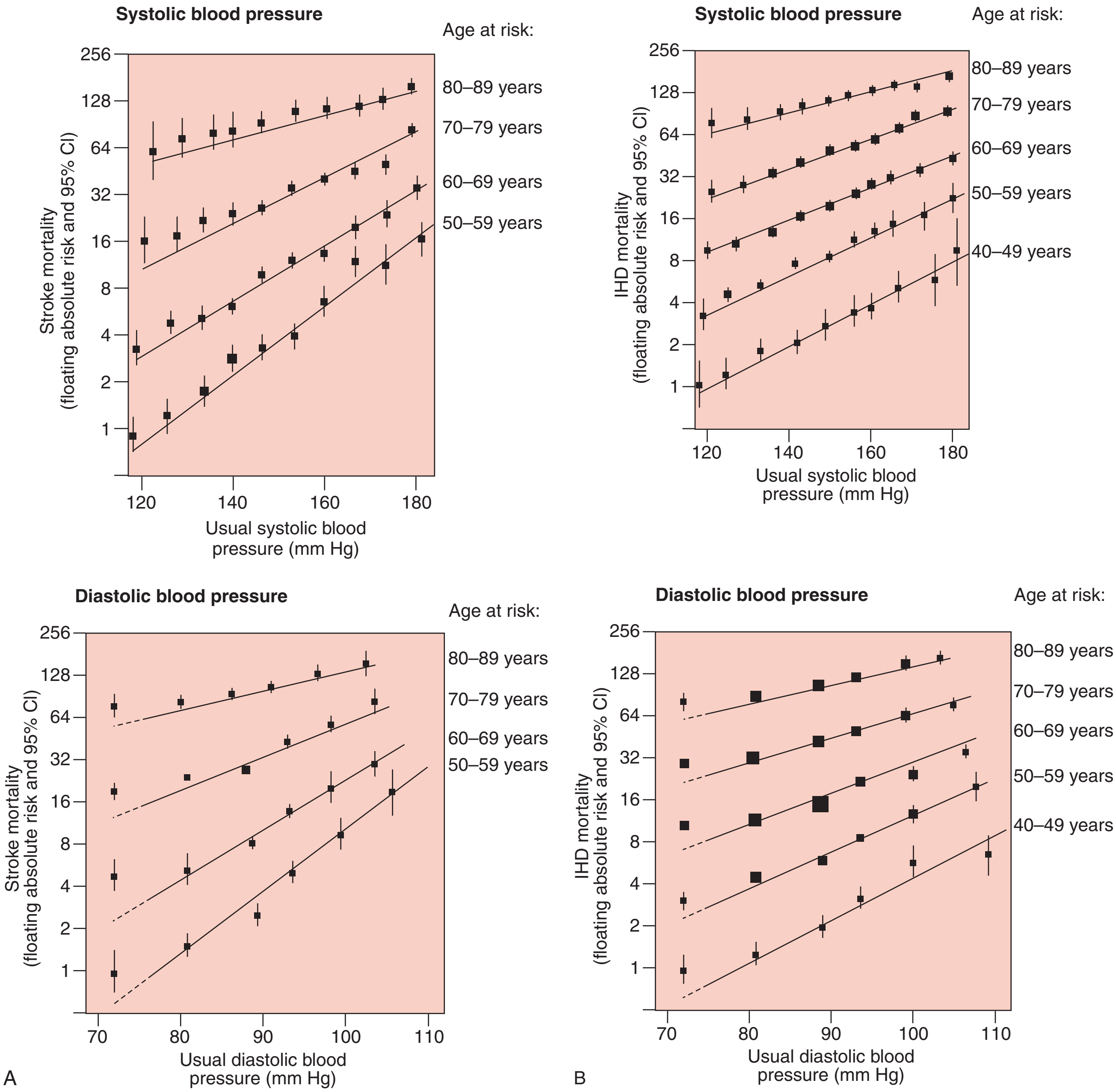


Figure 34–2 **A,** Stroke mortality rate in each decade versus usual blood pressure at the start of that decade. **B,** Ischemic heart disease (IHD) mortality in each decade versus usual blood pressure at the start of that decade. (Reprinted from Prospective Studies Collaboration: Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.)

interval = interval/paper speed). The average of the 10 heart beats is then used as the PWV. The other method is to use one of several automatic devices to measure the PWV [the Complior (Artech-Medical, Pantin, France), the SphygmoCor system (AtCor Medical, Lisle, Ill, USA), the CV Profilor device (Hypertension Diagnostics, Inc., Minneapolis), and the Wall Track System (Pie Medical, Maastricht, the Netherlands).[22]

Antihypertensive drugs from different classes have been shown to have differential effects on PWV, central aortic pressure, and PP, and some have concluded that these effects may be more important determinants of outcome than brachial arterial pressure per se.[17,21-26] The effects of short-term (4 weeks) administration of representatives of the four major classes of antihypertensive drugs on central aortic pressure and acute pressure augmentation were compared with each other and with placebo in a double-blind crossover study involving 32 previously untreated elderly patients with systolic hypertension.[17] Applanation tonometry was performed in the radial artery using the SphygmoCor apparatus. The patients received, in randomized order, a low-dose and then a high-dose placebo, 1 and 2 tablets; the BB atenolol, 25 and 50 mg; the ACEI perindopril, 4 and 8 mg or enalapril, 20 mg and 40 mg; the CCB felodipine, 5 and 10 mg or amlodipine, 5 and 10 mg; and the thiazide diuretic hydrochlorothiazide 25 and 50 mg.

Table 34–1 Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

High-Risk Conditions With Compelling Indications*	Recommended Drugs: Diuretic	β-Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist	Clinical Trial Basis†
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES
Post–myocardial infarction		•	•			•	ACC/AHA Post-MI Guideline, BHAT, SAVE, CAPRICORN, EPHESUS
High coronary disease risk	•	•	•		•		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE
Diabetes	•	•	•	•	•		NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease			•	•			NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	•		•				PROGRESS

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.
†Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.
AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; AIRE, Acute Infarction Ramipril Efficacy; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin receptor blocker; BHAT, β-Blocker Heart Attack Trial; CCB, calcium channel blocker; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Inbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation–American Diabetes Association; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial.
Reproduced from the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52. (See the JNC 7 Report for references to trials cited).

Interestingly, only the CCBs had dose-dependent effects on central and peripheral SBP; the other drug classes had flat dose responses. High-dose CCBs and diuretics caused greater reductions in brachial artery SBP than ACEIs or BBs; reductions in SBP were greater than in DBP, causing PP to fall (Fig. 34–4). Compared with central aortic pressures, brachial artery pressure measurements underestimated the change in SBP in patients on ACEIs and CCBs. The changes in PP were underestimated in patients on ACEIs and overestimated in patients on BBs. The PP reduction was statistically significant only for CCBs and diuretics. Heart rate was reduced by approximately 8 beats/min with BBs and was unaffected by other medications.

The first (outgoing pressure wave) peak in the systolic waveform was reduced by all drugs, but the decrease with CCBs was greater than with ACEIs or diuretics. The second (reflected pressure wave) peak in the systolic waveform was not reduced significantly by BBs, but was with the other three drugs. The peak aortic SBP and the aortic SBP at the end of ejection were lower with CCBs than with the other drugs. The augmentation pressures calculated from these data were reduced compared with placebo by ACEIs, CCBs, and diuretics, while the augmentation pressure on BBs was numerically but not statistically significantly higher than on placebo (Table 34–2). Augmentation indices tended to follow the same pattern (see Table 34–2), but the changes in augmentation indices were not as pronounced as the changes in augmentation pressure because of the differences in the central PP. On placebo, central aorta augmentation pressure and index were 23 mm Hg and 33.3%; on ACEIs the values were 18 mm Hg and 30%; on BBs, 26 mm Hg and 38.5%; on CCBs, 16 mm Hg and 28%; and on diuretics 17 mm Hg and 28.8%. Thus the augmentation pressure on BBs was statistically significantly greater than on the other three drug classes ($P < 0.05$), and numerically but not statistically greater than on placebo. The lowest central aortic pressures were achieved with CCBs and diuretics.

The major finding of this study is that the alteration in brachial artery BP with different drug therapies may not accurately predict the changes in central aortic pressure. Specifically, BBs reduced brachial but not central aortic SBP, while CCBs effected the greatest reductions in both central and peripheral pressures, and ACEIs caused greater reductions in central than peripheral pressures. These hemodynamic findings are consistent with the deleterious effects of BBs

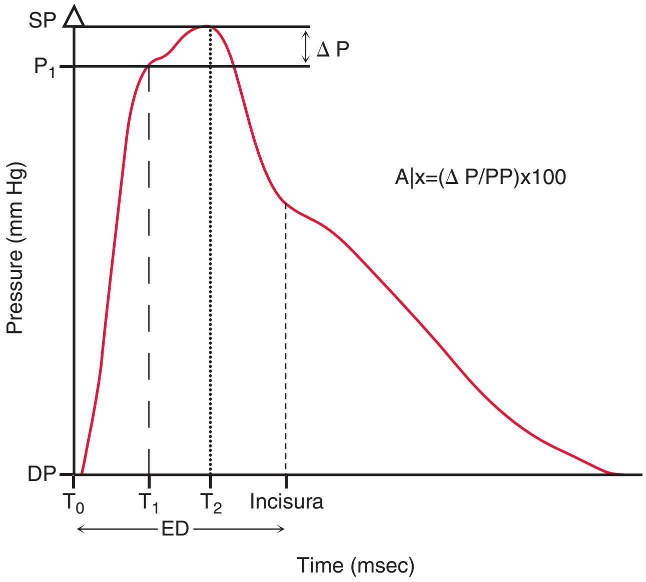


Figure 34–3 Hemodynamic parameters derived by pulse wave analysis of the central aortic pressure wave. T_0; time at the start of the waveform, T1; duration from start of waveform to the first peak/shoulder (outgoing pressure wave), T2; duration from start of waveform to the second peak/shoulder (reflected pressure wave), ED; ejection duration—duration from start of waveform to closure of the aortic valve (incisura), SP; central aortic systolic pressure, DP; central aortic diastolic pressure, P1; P1 Height—difference between the minimum pressure and the pressure at the first peak/shoulder (T1), augmentation (ΔP); difference between maximal pressure (central aortic systolic pressure) and pressure at the first peak/shoulder (P1 Height). (Reproduced from The CAFÉ Investigators for the ASCOT Investigators: Differential impact of blood pressure lowering drugs on central aortic pressure and clinical outcomes—principal results of the Conduit Artery Function Evaluation Study: The CAFÉ study. Circulation 2006;113:1213-25).

and the apparent benefits "beyond BP lowering" of CCBs and ACEIs observed in outcome studies.[21]

The pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd study (REASON) compared the effects of a low-dose combination of indapamide (0.625 mg) and perindopril (2 mg)(Per/Ind) with the BB atenolol (50 mg) on SBP, PP, aortic PWV (automatic measurements), and wave reflections (pulse wave analysis, applanation tonometry) in 471 patients with essential hypertension who were followed for 12 months.[23] For the same DBP reduction, Per/Ind decreased brachial SBP and PP significantly more than atenolol. Both antihypertensive agents decreased PWV to a similar degree, but only Per/Ind significantly attenuated carotid wave reflections, with resulting selective decreases in SBP and PP.

A subsequent report delineated the hemodynamic mechanisms underlying the selective central SBP reduction seen with Per/Ind in REASON (i.e., wave reflection and arterial stiffness) and determined whether these differ in the central and peripheral compartments of the arterial tree.[24] The selective effect of the Per/Ind regimen on central SBP became significant only after 1 year of follow-up, consistent with the known ability of the ACEIs to effect structural remodeling (reduced wall/lumen ratio) of distal muscular arteries and arterioles and to improve endothelial function and vascular smooth muscle tone. These structural changes would tend to alter (prolong) the transit time from the peripheral reflection

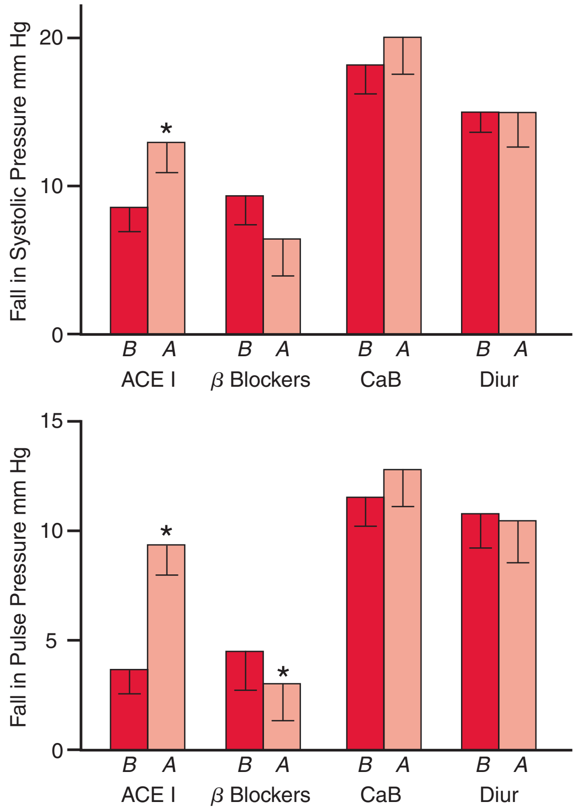


Figure 34–4 Fall in systolic blood pressure in the brachial artery *(B)* and aortic root *(A) (second peak)* and the fall in pulse pressure at the two sites with the different drug classes. ACE I, angiotensin-converting enzyme inhibitors; CaB, calcium blockers; Diur, diuretics. **P* < 0.05 compared with brachial artery values. (Reproduced from Morgan T, Lauri J, Bertram D, et al: Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004;17:118-23.)

Table 34–2 Differences in Augmentation Pressure and Index Among the Various Drug Groups. Augmentation Pressure Difference is Horizontal–Vertical Values; Augmentation Index Difference is Vertical–Horizontal Values

		Difference in Augmentation Index %			
		β	ACE I	Ca	Diur
Difference in Augmentation Pressure mm Hg	β		8.5%*	10.5%*	9.7%*
	ACE I	8*		2%	1.2%
	Ca	10*	–2		–0.8%
	Diur	9*	–2	–1	

**P*<0.05 (Bonferroni's corection).
From Morgan T, Lauri J, Bertram D, et al: Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004;17:118-23.

sites toward the central arteries and change the timing of incident and reflected waves, resulting in reductions in reflection coefficients of distal muscular arteries and arterioles and decreased amplitude of the backward pressure wave. All of these effects would contribute to reductions in central SBP with Per/Ind treatment compared with the BB without need to invoke alterations in PWV or LV ejection time, which were not observed in REASON.

A substudy of 146 subjects selected from the REASON study population compared the effects of the Per/Ind and atenolol regimens on echocardiographically determined LVM and related the changes in LVM to alterations in central and brachial SBP and PP.[25] At 1 year, reductions in LVM were greater with Per/Ind than with atenolol and were significantly linked to central, but not brachial, PP and SBP change and a longer delay in central return of wave reflections. This interesting observation provides a mechanistic explanation for previous findings that inhibitors of the RAAS reduce LVM more than BBs despite similar effects on brachial artery pressures and supports the general concept that hypertension-induced target organ damage and CVD morbidity/mortality are more closely related to central than peripheral BPs.

Differential effects of ACEI treatment on central and peripheral arterial pressures have been invoked to explain the impressive benefits of ACEI (ramipril) treatment in CVD prevention reported in the Heart Outcomes Prevention Evaluation (HOPE) trial, which could not be accounted for by reductions in conventional (cuff) brachial artery SBP and DBP.[26,27] Hemodynamic (cuff brachial artery pressure, central aortic pressure assessed by radial artery tonometry and PWV in aorta, upper limb, and lower limb arteries) responses to acute (5-hour) administration of ramipril, atenolol, and placebo were assessed in 30 patients in a randomized double blind trial.[26] Ramipril and atenolol treatment produced similar reductions in DBP in both brachial artery and aorta, but ramipril resulted in more than a 5 mm Hg greater reduction in aortic SBP. The aortic SBP reduction with ramipril was accompanied by a large reduction in the augmentation index, indicative of a reduction in peripheral wave reflection. There was also a differential effect of treatment on peripheral PWV (reduced with ramipril, unchanged with atenolol) but not aortic PWV, which paralleled the fall in DBP. Thus ramipril treatment was associated with decreased stiffness of peripheral but not central arteries. The authors concluded that the greater reduction in central versus brachial artery SBP could account for the clinical benefit of ramipril in the HOPE study, although other mechanisms including greater 24-hour BP reduction[28] also apply. This acute study raises the possibility that antihypertensive drugs elicit differential central BP responses, which may affect the outcome if sustained long term.

The Conduit Artery Function Evaluation (CAFÉ) study, a substudy of central arterial BP in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), is the first study to test the hypothesis that different antihypertensive drugs/drug combinations affect central aortic pressures differently despite similar effects on brachial BP in a major CV outcomes trial with repeated measurements throughout the study in a large cohort of patients.[21] Analyses of representative averaged radial artery waveforms and the resulting derived central aortic waveforms from individual patients with similar brachial BPs, treated with either atenolol or amlodipine monotherapy in the CAFÉ study, show clear differences in the morphology of both the radial and central aortic arterial waveforms (Fig. 34–5). Atenolol monotherapy was associated with a broader peripheral waveform and a more prominent late systolic peak in the central aortic waveform. Final results of the CAFÉ study revealed significantly greater reductions in central aortic SBP and PP with CCB ± ACEI compared with BB ± diuretic treatment despite similar brachial BP measurements. Coupled with the impressive clinical benefits of the CCB ± ACEI treatment regimen in the ASCOT BP lowering trial,[29] these findings lend strong support to the concept that central arterial pressure is clinically important in assessing prognosis and treatment responses in hypertensive patients.

A meta-analysis of placebo-controlled outcome trials involving more than 15,000 older persons with ISH showed overall reductions of 13% in all-cause mortality and 18% in CV mortality from active treatment compared with placebo.[30] For nonfatal and fatal outcomes combined, active treatment resulted in reductions of 26% for all CV endpoints, 30% for stroke, and 23% for MI including sudden cardiac death. The number of patients needed to treat (NNT) for 5 years to prevent one major CV event was lower in men (18 vs. 38), in those older than age 70 (19 vs. 39) and in those with pre-existing CVD (16 vs. 37). These results show that antihypertensive treatment is highly effective in preventing CVD morbidity and mortality in elderly persons with ISH.

DIASTOLIC BLOOD PRESSURE AND CARDIOVASCULAR DISEASE RISK

Reductions in DBP have been observed in large studies to correlate with reduced stroke and CHD risk.[31,32] For example, in 9 prospective observational studies of 420,000 individuals, reductions of 5, 7.5, and 10 mm Hg were shown to be associated with 34%, 46%, and 56% less stroke and 21%, 29%, and 37% less CHD, respectively.[31] Early outcome trials of antihypertensive treatment involving large numbers of patients used decreases in DBP to establish reductions in risk of both stroke and coronary events. In 14 unconfounded, randomized trials of 37,000 individuals treated for an average of 5 years, a decrease in DBP of 5 to 6 mm Hg was associated with 35% to 40% less stroke and 20% to 25% less CHD, respectively.[32]

Although increased peripheral vascular resistance leads to increases in both SBP and DBP, increased arterial stiffness leads to an increase in SBP and a decrease in DBP.[12,14] DBP is influenced by arterial resistance and stiffness, both of which are independent risk factors for CVD. Changes in BP with aging reflect the evolution of alterations in both structure and function of the arterial system.

Current guidelines recommend goal BPs previously considered below normal, leading to a growing concern that some persons are being overtreated and are experiencing more CVD events due to a lower DBP, the “J-curve phenomenon”.[33] For the past 10 to 20 years, there has been considerable debate over the existence of a J-curve. Explanations that have been offered to account for a J curve of DBP include the following:

1. Aggressive treatment of HTN in patients with underlying CHD compromises coronary perfusion, which occurs almost exclusively during diastole, leading to tissue ischemia and subsequent coronary events.

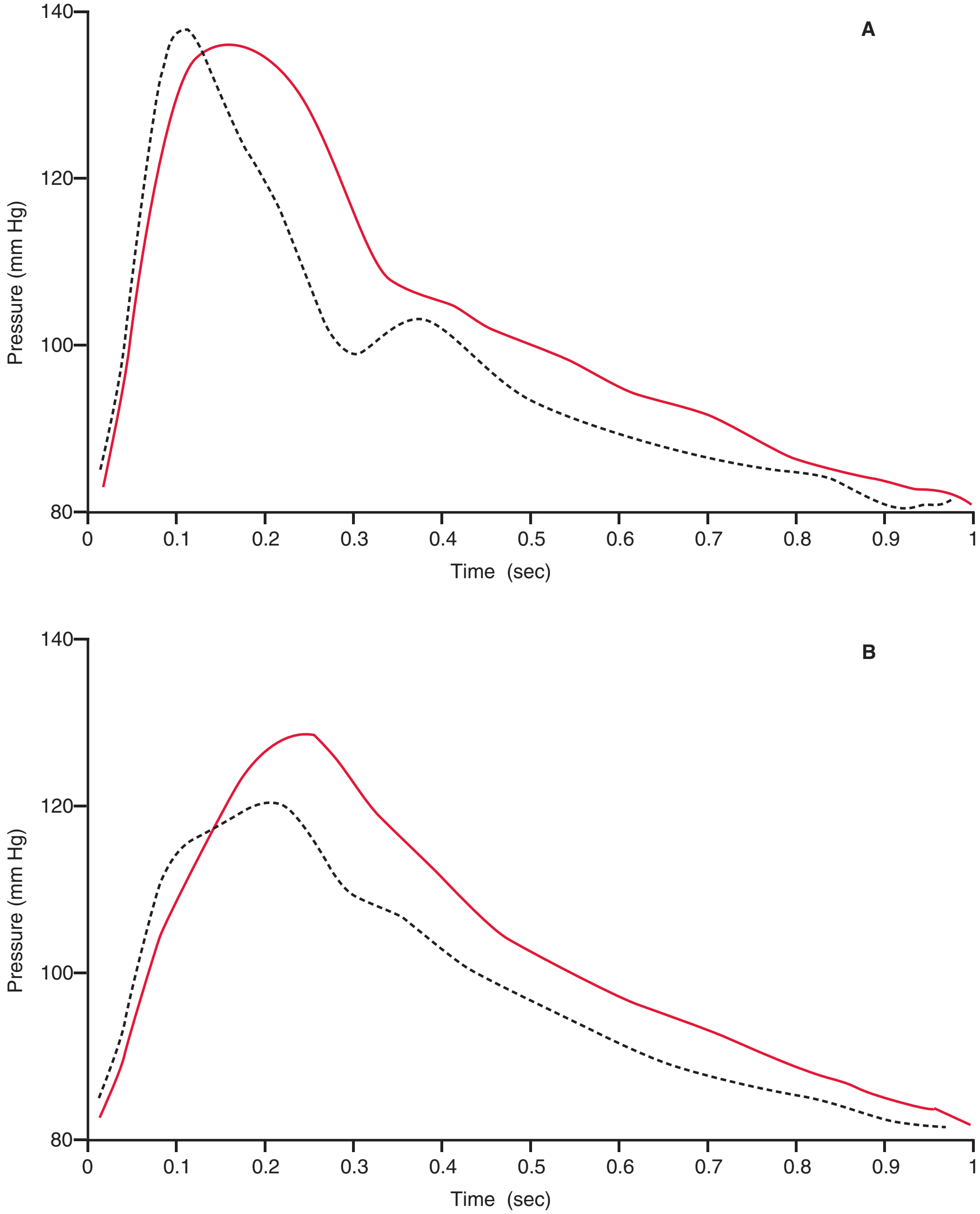


Figure 34–5 Examples of **(A)** peripheral and **(B)** corresponding derived central aortic waveform from patients of equal age treated with atenolol *(solid line)* or amlodipine *(dashed line),* as monotherapy, achieving equivalent brachial blood pressures. (Reproduced from The CAFÉ Investigators for the ASCOT Investigators: Differential impact of blood pressure lowering drugs on central aortic pressure and clinical outcomes—principal results of the Conduit Artery Function Evaluation study: The CAFÉ study. Circulation 2006;113:1213-25.)

2. Excessively low DBP results from increased PP due to progressive stiffening of the central arteries and advancing atherosclerotic disease. In particular, the increased PWV seen in older persons can lead to arrival of the pressure wave before closure of the aortic valve and a lower aortic DBP, resulting in a loss of any "boosting" effect to the coronary circulation.[15,16]
3. The poor autoregulatory reserve of the coronary circulation, especially in the presence of rigid atherosclerotic arteries, and the increased oxygen requirement of the hypertrophic LV in hypertensive patients enhance the probability of developing ischemia and CVD events when DBP falls.
4. The adverse metabolic effects of antihypertensive therapy (i.e., hypokalemia, hyperglycemia, and hyperlipidemia) could become more important at low levels of coronary perfusion, thus favoring a J-shaped relationship for cardiac events.

Studies that have looked for a J-shaped relationship between DBP and CVD events have yielded mixed results, in part dependent on the patient population studied.[33-42] A study by

Cruickshank supporting the existence of a J-curve involved 902 patients with moderate to severe HTN who received a BB (atenolol) alone or with other antihypertensive agents, such as a thiazide diuretic, a vasodilator (hydralazine or prazosin, and nifedipine), or methyldopa or bethanidine as needed to achieve a BP of 140/90 mm Hg.[33] The mean initial BP was 183/109 mm Hg, and the mean BP on treatment was 145/87 mm Hg. Results were analyzed by DBP group (>90 mm Hg, 85 to 90 mm Hg, and < 85 mm Hg), and by whether CHD was present or absent. An increase in mortality from MI was found in patients with CHD at DBP levels below 85 to 90 mm Hg, while no increase in mortality was noted in these patients at DBP > 85 mm Hg or in those without CHD.

A subsequent meta-analysis of data from 13 outcome studies of antihypertensive treatment that included more than 48,000 participants addressed the question of whether there is a point beyond which BP (mainly DBP) reduction is no longer beneficial and possibly even deleterious.[34] Although no consistent J-shaped relationship between treated BP level and stroke incidence or mortality was seen, studies consistently demonstrated a J-shaped relationship between treated DBP and cardiac event incidence and mortality. SBP relationships often were not addressed or gave conflicting results. The authors observed that treated DBPs below the beneficial therapeutic threshold point of 85 mm Hg were associated with increased risk of cardiac events. They further noted that, as in the Cruickshank study, the J-shaped relationship appeared to be most marked in subjects with preexisting cardiac disease and was observed consistently in untreated or placebo-treated control subjects, as well as treated individuals. Their main conclusion was that the J-curve is probably independent of treatment and that it reflects a relation between cardiac events and absolute DBP, with treatment merely shifting ischemic hypertensive patients from a fairly safe part to a less safe part of the curve, where cardiac mortality is increased. Although acknowledging the limitations of their data (i.e., the lack of a randomized trial that evaluates different treatment thresholds and targets), the authors suggested that prudence dictates caution in lowering DBP levels below 85 mm Hg in patients with known ischemic heart disease.

The Hypertension Optimal Treatment (HOT) study is the only randomized prospective outcome trial that has tested the J-curve hypothesis in a rigorous fashion. A goal of HOT was to determine the optimal target DBP in the treatment of HTN.[35] A total of 18,790 patients between 50 and 80 years old with DBP between 110 and 115 mm Hg were assigned at random to three DBP target groups (DBP ≤ 90, ≤ 85 or ≤ 80 mm Hg, respectively). Baseline therapy was a dihydropyridine CCB (felodipine) with a five-step titration scheme including the addition of an ACEI or BBs and, if necessary, a diuretic. At the end of the study, DBP was reduced by 20.3, 22.3, and 24.9 mm Hg in the ≤ 90 mm Hg, ≤ 85 mm Hg, and ≤ 80 mm Hg target groups, respectively. The lowest incidence of major CV events occurred at a DBP of 82.6 mm Hg, while the lowest risk of CV mortality occurred at a DBP of 86.5 mm Hg. Although the study failed to demonstrate a significant benefit in lowering BP below approximately 140/85 Hg in nondiabetic patients with CHD, no adverse effects of intensive treatment of BP were seen (i.e., no J-curve).

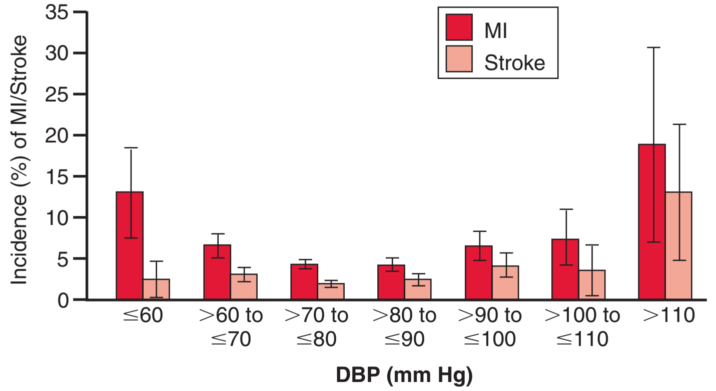
The diabetic subgroup in the HOT trial did benefit significantly from aggressive BP lowering, however. Among the 1501 diabetic patients, a significant 50% reduction in major CV events and CV mortality ($P = 0.005$ and $P = 0.016$) was seen in those randomized to a target DBP of ≤ 80 mm Hg compared with the target group ≤ 90 mm Hg. **On the basis of these data and data from other large, randomized, controlled trials that have provided evidence that patients with diabetes achieve greater reductions in risk of major CVD events and CV death with regimens targeting lower BP goals,[36] intensive BP lowering to a goal of < 130/80 mm Hg is recommended for hypertensive diabetic patients.[8] However, in patients with known CHD, a DBP lower than 80 mm Hg may lead to an increase in cardiac events.**

Evidence for a J-curve has been shown in the elderly population with ISH, as well as in patients with established CHD. Examination of the effect of DBP on CVD events in SHEP participants demonstrated that in the active treatment group (2358 subjects), a 5-mm Hg decrease in DBP was associated with increased stroke (relative risk [RR] 1.14; 95% CI: 1.05 to 1.22, $P < 0.01$), CHD (RR 1.08; 95% CI: 1.00 to 1.16, $P < 0.05$), and CVD (RR 1.11; 95% CI: 1.05 to 1.16, $P < 0.01$).[37] Significant adverse events were first observed at a DBP of 70 mm Hg and were more noticeable at lower DBP (DBP ≤ 60 mm Hg). This effect was seen only with CVD and only in the treated group. The results of this study suggest that in older persons with ISH, a DBP < 70 mm Hg (or perhaps < 60 mm Hg) is a risk factor for future adverse CVD events.

Analysis of data from the MRC Mild Hypertension Trial confirmed that the predicted risk of a CHD event exhibits a J-shaped relationship with DBP, while stroke risk declines continuously as DBP falls within the physiologic range.[38] Hence patients with the greatest PP are at highest risk for CHD events but not for stroke across the range of SBP. The mechanisms linking PP to increased CHD risk include increased arterial wall stiffness, increased PWV, and early return of the reflected pressure wave to the heart, all of which tend to increase LV work and oxygen requirements and diminish coronary perfusion. In contrast, cerebral blood flow occurs throughout the cardiac cycle and the relationship between PP and stroke is weak (i.e., there is no J-curve for stroke). The authors speculated that this may explain why most trials in hypertension have shown a greater benefit of treatment on stroke than on CHD events.

Broader applicability of the J-curve concept was found in a meta-analysis of 7 randomized clinical trials from the INdividual Data ANalysis of Antihypertensive (INDANA) intervention database, which included 40,233 persons with hypertension, of whom 1655 died during a trial.[39] A J-shaped relationship between DBP and risk for death was observed for total and cardiovascular mortality in treated patients (nadir, 84 and 80 mm Hg, respectively) and untreated patients (nadir, 90 and 85 mm Hg, respectively). For noncardiovascular deaths, the relationship was J-shaped in the treated group (nadir, 84 mm Hg) only. Similar results were observed for SBP. Thus the increased risk for events observed in patients with low BP was not related to antihypertensive treatment and was not specific to BP-related events. The authors concluded that reverse causality (i.e., poor health conditions leading to low BP and an increased risk for death) probably explains the J-shaped curve.

The original and offspring Framingham cohorts have been prospectively analyzed for the occurrence of a J-curve relating BP to CVD risk.[40] Over 12 years of follow-up, a significant increase in CVD events was discovered at DBP < 80 mm Hg;



MI							
Patients with MI(n)	23	135	387	255	71	14	8
Total patients (n)	177	2239	11324	7378	1214	201	43
Mean SBP (mm Hg)							
Patients with MI	127.0	131.9	135.2	143.8	158.3	166.9	191.4
Patients without MI	126.2	129.6	131.4	139.3	155.2	170.3	185.7
Stroke							
Patients with stroke (n)	4	50	151	116	44	5	6
Total patients (n)	175	2253	11320	7366	1217	199	45
Mean SBP (mm Hg)							
Patients with stroke	112.2	132.7	136.3	143.8	161.1	171.1	177.9
Patients without stroke	126.7	129.6	131.5	139.3	155.2	169.9	187.9

Figure 34–6 Incidence of Total MI and Total Stroke by DBP Strata. Modified from Messerli FH, Mancia G, Conti CR, et al: Dogma Disputed: The J-Curve in Hypertensive Patients With Coronary Artery Disease: The International Verapamil-Trandolapril Study (INVEST). (Reproduced from Messerli FH, Mancia G, Conti CR, et al: Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006;144:884-93).

however, this was only evident in those persons with a concomitant SBP of > 140 mm Hg and, consequently, a PP of > 46 mm Hg, consistent with the concept that the alterations in central BP dynamics and pulse wave reflection described previously are responsible for the J-curve.

The International Verapamil-Trandolapril Study (INVEST) was a randomized, open label study of 22,576 patients with HTN and known CHD aged 50 years and older.[41] In INVEST, the relationship between average on-treatment (verapamil SR or atenolol-based) BP and risk for the primary outcome (all-cause death, nonfatal stroke, nonfatal MI), all-cause death, and total MI, but not total stroke was J-shaped, particularly for DBP, with a nadir at 119/84 (Fig. 34–6).[42] Although the J-curve was relatively shallow for SBP, lower DBP led to nearly doubling and tripling of the risk for primary outcome in the DBP strata > 60 to ≤ 70 mm Hg and ≤ 60 mm Hg. At lower DBP there was a significant preponderance of MIs over strokes. A significant interaction for the primary outcome was observed with decreased DBP and history of revascularization; low DBP was associated with relatively lower risk of the primary outcome in revascularized compared with nonrevascularized patients. Findings from this large trial in which all enrollees had hypertension and CHD reinforce the conclusion that there is a prominent J-curve for the relationship between treated DBP and CHD events in this high-risk population, in whom DBPs below 70 to 80 mm Hg could be harmful.

CHRONOBIOLOGY AND CORONARY HEART DISEASE

Appreciation of the diurnal rhythm of BP and CVD events has given rise to the development of chronotherapeutic agents, specifically formulated drug delivery systems designed to provide drug concentrations that vary in synchrony with biological needs, thus enhancing both the efficacy and safety of treatment. An example of such a chronotherapeutic agent is a controlled-onset extended release CCB (COER-verapamil) that is taken at bedtime and allows lower drug concentrations during sleep and maximal drug delivery during the early morning hours.[43] The chronotherapeutic approach was not shown to be superior to conventional treatment in the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Trial.[44] However, the results of this trial are inconclusive due to the premature termination of the study for nonmedical reasons.

Differences in efficacy or adverse effects depending on the circadian time of administration have been clearly identified for a variety of BP-lowering drugs and drug combinations.[45] In particular, evening dosing of standard antihypertensive agents has become useful as an alternative chronobiologic strategy for lowering BP. This is especially important for patients with the nondipper BP pattern (<10% decline in nocturnal mean relative to diurnal mean BP), which is associated with target organ damage including LVH, AMI, stroke, albuminuria, and progression to ESRD, as well as with other CVD risk factors (e.g., fibrinogen levels). Nondipping BP patterns are also associated with the absence of 24-hour therapeutic coverage in patients treated with single morning doses of antihypertensive drugs. A study that investigated the impact of treatment time on BP control, circadian BP pattern, and biochemical indices of CVD risk in patients with resistant hypertension revealed significant reductions in 24-hour mean SBP and DBP, particularly prominent reductions in nighttime BPs and decreases in prevalence of nondipping, in patients taking one drug at bedtime compared with those taking all drugs on awakening (Fig. 34–7).[46] Importantly, BP control rates in subjects who were dosed at

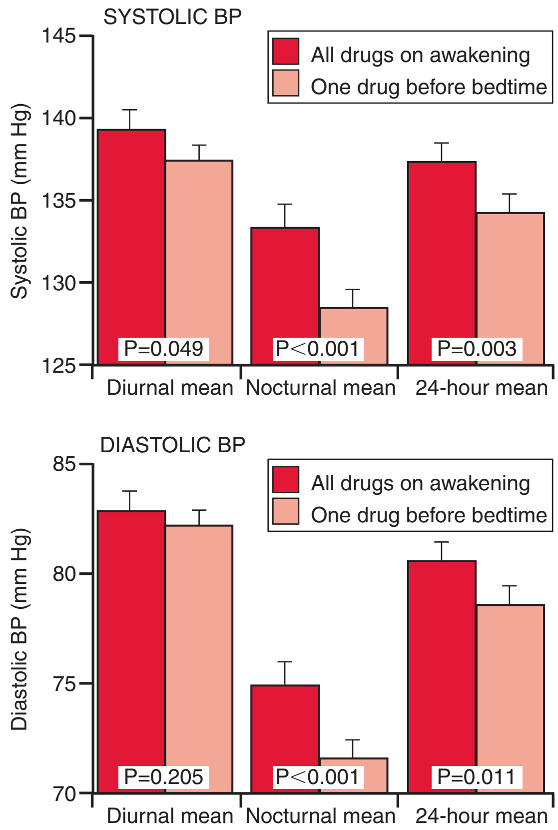


Figure 34–7 Diurnal, nocturnal, and 24-hour means of systolic blood pressure *(top)* and diastolic blood pressure *(bottom)* in patients with resistant hypertension receiving all antihypertensive drugs on awakening, or receiving 1 of the drugs at bedtime, studied by 48-hour ABPM. (Reproduced from Hermida RC, Ayala DE, Calvo C, et al: Effects of time of day of treatment on ambulatory blood pressure pattern of patients with resistant hypertension. Hypertension 2005;46:1053-9.)

bedtime were almost double those seen in patients who received all of their drugs on awakening. Those who took one drug at bedtime also showed significant reductions in glucose, cholesterol, and fibrinogen levels, as well as urinary albumin excretion. Although the effects of antihypertensive treatment time on CVD outcomes have not been formally tested in a randomized trial, some have attributed the impressive benefits of ramipril in the HOPE trial, at least in part, to evening dosing of the drug.[28]

CORONARY HEART DISEASE: CHRONIC STABLE ANGINA AND SILENT ISCHEMIA

Hypertensive patients with chronic stable angina are at particular risk due to the enhanced myocardial oxygen demand created by increased BP (SBP in particular) and HR.[47] Persons with both stable angina (with or without silent ischemic episodes) and HTN derive particular benefit from treatment with BBs and CCBs.[48] The pharmacologic treatment of chronic stable angina has evolved into a two-armed approach (Fig. 34–8). The first arm includes the agents aimed at reducing angina (BBs, CCBs, and nitrates). The second arm includes agents that slow the progression of atherosclerosis, stabilize atherosclerotic plaque, and promote the health of the vascular endothelium.[47] When planning a regimen of therapy for persons with HTN and CAD, pharmacologic agents from both arms should be employed.

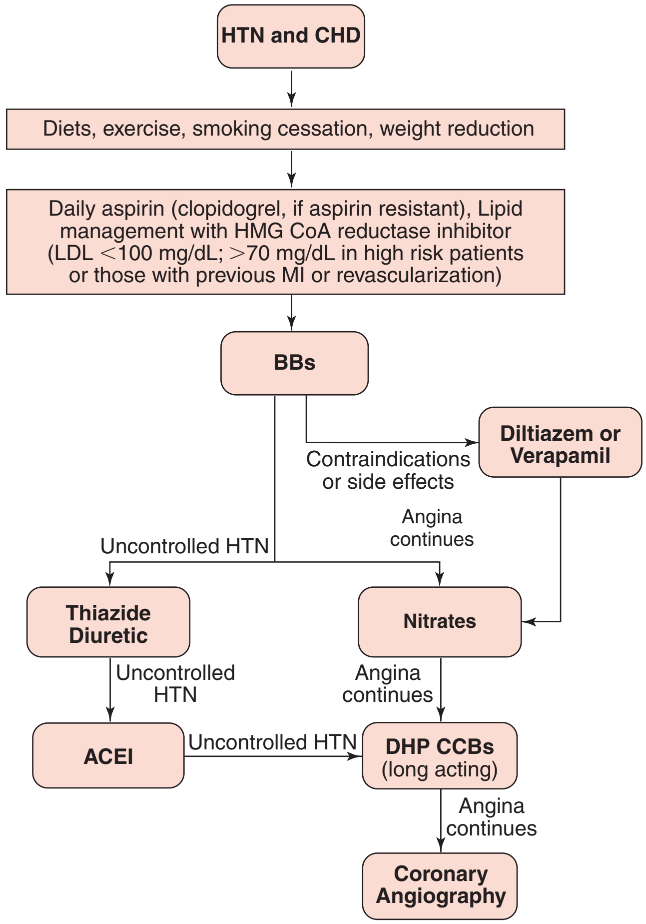


Figure 34–8 Algorithm for the management of a patient who presents with hypertension and angina. Doses of drugs should normally be titrated to the usual maximal dose before a second agent is tried. The recommended calcium antagonists are cardiac-slowing agents, such as verapamil or diltiazem. Inadequate control of angina is defined as continuing limiting symptoms. Inadequate control of hypertension is defined as blood pressure above goal.

The goals of treating patients with HTN and angina are to lower BP, reduce ischemia, relieve chest discomfort, and prevent future CVD events. Pharmacologic therapy should be initiated with a BB unless contraindicated. In variant (Prinzmetal's) angina, the treatment of choice is a dihydropyridine CCB. BBs are first-line agents in the treatment of patients with coexisting HTN and angina.[47,48] Beneficial effects for the patients include reduction of myocardial oxygen consumption and enhancement of coronary flow. Although, for the reasons stated earlier, concomitant angina is a compelling indication for BB use in hypertensive patients, meta-analyses of randomized controlled outcome trials of antihypertensive treatment have found that BB-based treatment is no better than placebo for prevention of CVD outcomes.[49,50] Accordingly, many authorities no longer recommend BBs as

first-line treatment for hypertensive patients in the absence of compelling indications (HF, post MI, high CHD risk, angina) for their use.[50a]

If angina continues, long-acting CCBs can be added to the regimen. CCBs decrease total peripheral resistance, which leads to a decrease in BP and in wall tension, thus reducing myocardial O_2 consumption. CCBs also decrease coronary resistance (helpful in relieving spasm, which may be associated with Prinzmetal's angina) and enhance poststenotic coronary perfusion, which increases myocardial O_2 supply. **Nondihydropyridine CCBs have the additional benefit of decreasing heart rate. Short-acting dihydropyridine CCBs should be avoided due to increased mortality, particularly in the setting of acute MI.[51] Although nondihydropyridine CCBs can be used as antianginals in combination with a BB, there is an associated risk due to the potential for severe bradycardia or heart block, or both.**

Long-acting dihydropyridine CCBs are effective antianginal agents and do not share the disadvantage of bradycardia/heart block. Therefore if a CCB is necessary in addition to a BB to control angina in a hypertensive patient, it should be a long-acting dihydropyridine CCB.[48] The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial showed no difference between amlodipine and enalapril in the occurrence of the primary endpoint of CV death, nonfatal MI, revascularization, hospitalization for angina or HF, cardiac arrest, stroke, or PAD in patients with CHD and normal BP or prehypertension.[52] In an intravascular ultrasound subgroup analysis, amlodipine appeared to have a significant retarding effect on atheroma progression in those with higher BPs that was not seen with enalapril or placebo. Data from the ALLHAT, VALUE, and ASCOT trials have demonstrated that it is safe to use dihydropyridine CCBs in high-risk hypertensive patients without concern for a higher morbidity or mortality, or both, from a CV cause.[29,53,54] If angina is not controlled on a BB-CCB regimen, nitrates can be added.

Use of ACEI in high-risk persons (those with a history of CHD, stroke, PAD, DM) with a normal LVEF and no evidence of HF or LV dysfunction has been shown to be beneficial in the Heart Outcomes Prevention Evaluation (HOPE) trial.[27] Patients randomized to an ACEI (ramipril) had significantly fewer MIs, strokes, or deaths from CV causes and were less likely to require revascularization or hospitalization for unstable angina or for complications related to DM. Patients randomized to ramipril also had fewer cardiac arrests, less angina, and less HF compared with placebo. On the basis of these positive findings, ACEIs became widely prescribed for all patients with vascular disease.

The HOPE–The Ongoing Outcomes (HOPE-TOO) trial assessed whether the benefits observed during the HOPE trial were sustained during an additional 2.6 years of follow-up after trial cessation.[55] During the post-trial follow-up, despite similar rates of use of ACEIs in the two groups (72% ramipril vs. 68% placebo), patients originally allocated to ramipril had a 19% further reduction in relative risk of MI, a 16% reduction in risk of revascularization, and a 34% reduction in risk of new-onset DM, independent of baseline risk and ancillary treatments. There was no difference in stroke or CV deaths. The investigators concluded that the ACEI likely had favorable effects on endothelial function, vascular structure/function, and glucose metabolism that were sustained beyond the blinded period of the trial and that ACEIs may provide lifelong preventive benefit. They urged longer-term follow-up of prevention trials in order to obtain better estimates of long-term effects (benefits) of treatment.

The vast majority of patients in HOPE were not hypertensive (average BP was 139/79 for both groups) during the trial, and the benefits of the ACEI were reported by the investigators to be greater than could be accounted for by the reduction in BP seen with ramipril treatment. The conclusion that the benefit of the ACEI in HOPE was independent of BP has been challenged on the basis of the manner in which BP was monitored in the trial and the finding of a large (–10/4 mm Hg over 24 hours, –17/8 mm Hg during nighttime) reduction in BP in the ramipril group compared with placebo in a substudy that used ambulatory blood pressure monitoring (ABPM).[28] Importantly, participants in HOPE were instructed to take the study drug at bedtime, perhaps exploiting the benefit of a peak BP effect of the ACEI in early morning.

The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) compared perindopril with matched placebo in 12,218 persons with stable CHD, the majority of whom had experienced a prior MI or had been revascularized, or both.[56] Most patients were on antiplatelet therapy, BBs, and lipid-lowering therapy. The primary endpoint, a composite of CV death, MI, or cardiac arrest, was reduced significantly in the perindopril group compared with the placebo group. The number needed to treat (NNT) with perindopril for 4 years to prevent one CVD event was determined to be 50. Based largely on the results of this trial, perindopril was given FDA approval for the indication of reducing CV mortality and nonfatal MI in patients with stable CHD.

The Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial compared trandolapril with placebo in 8290 persons with preserved LV function and stable CHD.[57] The primary endpoint was a composite of cardiovascular death, MI, or revascularization. In contrast to HOPE and EUROPA, no significant difference in outcomes was demonstrated between the ACEI and placebo groups in PEACE. The negative findings of PEACE have been attributed to low event rates: the placebo group in PEACE had lower event rates than either the placebo or active treatment group in HOPE (Fig. 34–9). In fact, the annualized rate of death from all causes in PEACE was similar to that of an age- and sex-matched general population. The fall in event rates likely resulted from more intensive management of risk factors and underlying CVD. At baseline, 70% of the patients in PEACE (vs. 29% in HOPE and 56% in EUROPA) were receiving lipid-lowering therapy, and 72% of patients in PEACE, as compared with 54% in EUROPA and 40% in HOPE, had undergone coronary revascularization before enrollment. **The results of the PEACE trial provide evidence that CHD patients with preserved LV function who are receiving intensive medical therapy and revascularization, in whom rates of CVD events are low, may not derive further benefit from ACEI treatment. However, as in HOPE and EUROPA, only a minority of patients enrolled in PEACE had documented hypertension. The presence of CHD in a person with hypertension remains a compelling indication for ACEI therapy.[8]**

Some evidence indicates that ARBs may be less effective than ACEIs in reversing endothelial dysfunction and preventing coronary events, and it has even been suggested that

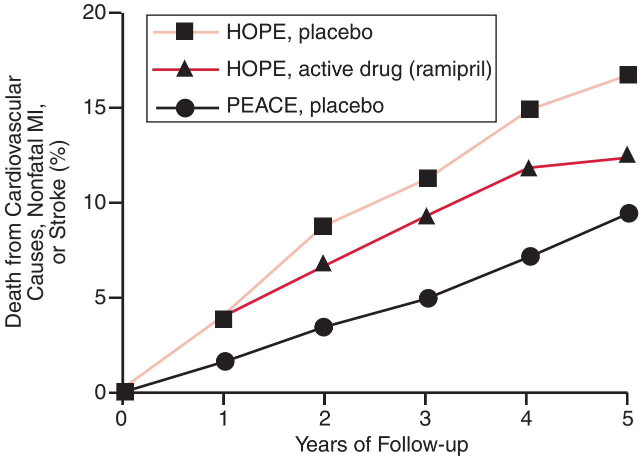


Figure 34–9 Comparison of Outcomes in the PEACE and HOPE trials. (Reprinted from The PEACE Trial Investigators: Angiotensin-converting enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058-68.)

use of ARBs may be associated with higher rates of MI.[58] To examine these issues, a meta-analysis of 19 controlled clinical trials with 31,569 participants that compared ARBs with ACEIs or placebo has been carried out.[59] Of note, only two of these studies examined the use of ARBs in hypertensive patients; others focused on patients with diabetes and nephropathy, HF, or recent MI/ischemic syndrome. Use of ARBs was not associated with a statistically significant increased risk of MI compared with either placebo or ACEIs. The 95% confidence limits of the statistical analysis did not exclude an increase of up to 16% or a decrease of up to 25% in risk of MI, however. The ARB-placebo comparison included the CHARM-Alternative trial, the only study to show a statistically significant increase in MI rates with ARB treatment.[60] CV mortality fell with ARB treatment in CHARM-Alternative, despite the increase in MI, and there was no increase in MI with ARB treatment in other HF trials, including CHARM-Added[61] and ValHEFT.[62] Thus this analysis showed neither benefit nor harm of ARB treatment compared with placebo in prevention of acute MI. The ARB-ACEI comparison was driven by the large post-MI OPTIMAAL trial,[63] in which the ARB losartan was not found to be superior or noninferior to the ACE inhibitor captopril with respect to overall mortality. Data from the larger VALIANT trial[64] were not available for analysis, and the LIFE[65] and VALUE[54] trials were excluded because they lacked placebo or ACEI control groups.

A meta-analysis by the Blood Pressure Lowering Treatment Trialists examined 3 large-scale randomized outcome trials including over 18,000 participants with acute myocardial infarction or HF that made direct head-to-head comparisons between ACEIs and ARBs.[66] They found no differences between ACEI and ARB treatment for any outcome. Since no head to head ACEI-ARB comparison trials in patients with HTN and/or increased risk of CVD are available, the Trialists carried out meta-regression analyses of relative risk reductions and corresponding followup BP differences in trials that compared the effects of ACEI or ARB treatment to treatment with placebo or an active comparator.[66] Data from 26 trials including over 146,000 patients with analyzed. The meta-regressions provided indirect evidence that for CHD outcomes, ACEIs but not ARBs provided risk reduction beyond that achieved by BP lowering. This relationship did not hold for other outcomes (i.e., stroke and HF). Limitations of the meta-analysis, acknowledged by the authors, include the indirect nature of the class comparisons and the absence of a direct confirmatory result from a head-to-head comparison of ACEI vs. ARB treatment in a high risk population.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) will provide the first head to head comparison of ACE inhibitor versus ACE inhibitor–ARB combination and ARB versus placebo treatment in high-risk patients with underlying CVD.[67] Pending the results of these trials, compelling indications for the use of ACE inhibitors or ARBs in hypertensive patients are largely overlapping.[8] The major advantage of the ARB class is that its side effect profile resembles that of placebo. Acute renal failure, hyperkalemia, cough, and angioedema are rare with the ARBs.

CORONARY HEART DISEASE: ACUTE MYOCARDIAL INFARCTION

Elevated BP can contribute to the occurrence of an acute coronary syndrome because increased shear forces from sudden changes in pressure can cause plaque fissuring. Increased sympathetic tone and catecholamine release contribute to both BP elevation and increased wall tension, which worsens ischemia by increasing O_2 demand, and can precipitate acute MI.[68] The presence of antecedent HTN increases the risk of MI twofold to threefold.[69] The increased risk of CHD in hypertensive patients is also related to the high frequency (30% to 40%) of associated risk factors (hypercholesterolemia, DM, tobacco use, and obesity) in this patient population. A history of HTN in patients who have had an MI is an independent risk factor for reinfarction and may confer an increased risk of mortality in the hospital, as well as following discharge.[69-71]

The goals of therapy in hypertensive patients with MI are to control BP, pain, and HR; reduce morbidity and mortality; and decrease the likelihood of future CVD events (Fig. 34–10). BBs (non-ISA) are first-line agents for patients with coexisting MI and HTN. Their benefit in this setting is related to their ability to limit infarct size, decrease the risk of recurrent MI, improve survival, and decrease the incidence of sudden cardiac death (believed to be due to fatal arrhythmias).[72-75] Common adverse effects and precautions regarding use of BBs in hypertensive patients with CVD are listed in Table 34–3.

The combined α- and β-adrenergic blocker carvedilol was studied in a post-MI population of 1959 patients with LV dysfunction in the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial.[76] All patients had a proven MI and LVEF ≤ 40%. CAPRICORN was not a hypertension trial, but more than 50% of patients in CAPRICORN were also hypertensive. Over a mean follow-up period of 1.3 years, all-cause mortality, CVD mortality, nonfatal MI, and all-cause mortality or nonfatal MI were lower in the carvedilol group than in the placebo group. The 23% observed reduction in mortality was in addition to the benefits conferred by ACEI and reperfusion therapies, which were prescribed in 98% and 46% of the patients, respectively. CAPRICORN is the first

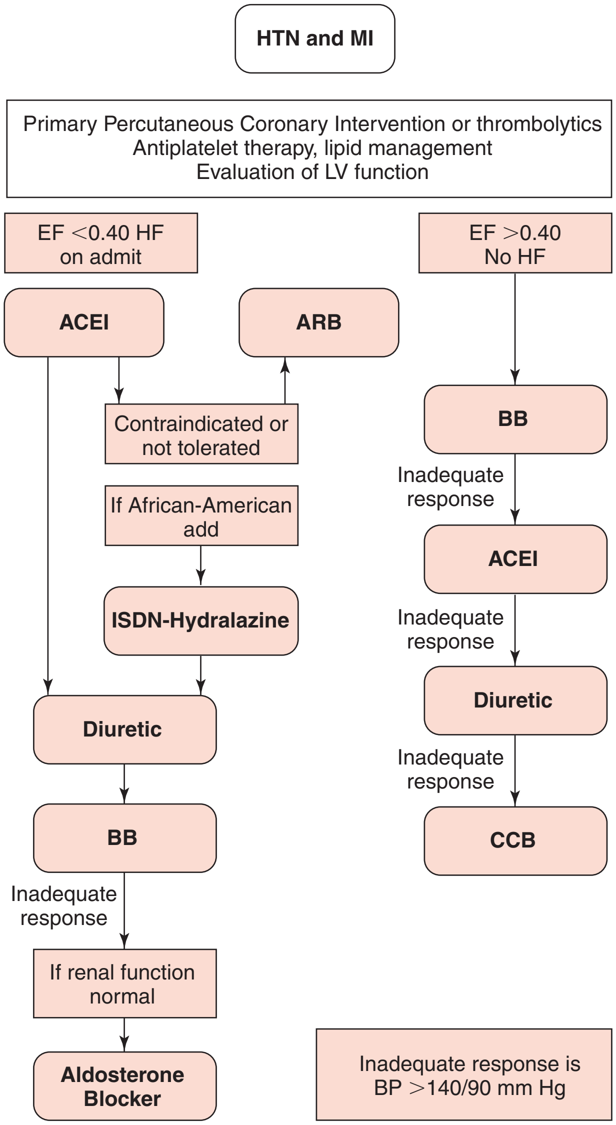


Figure 34–10 Algorithm for the management of hypertension in a patient with a myocardial infarction. Doses of drugs should normally be titrated to the usual maximal dose before a second agent is tried. The recommended calcium antagonists are cardiac-slowing agents, such as verapamil or diltiazem.

study to demonstrate the beneficial effects of BBs post-MI in the postreperfusion era. It also shows the benefit conferred on post-MI patients with LV dysfunction—a population excluded from prior BB trials in acute MI.

In the setting of acute MI, CCBs can be used in situations where BB therapy is inadequate to control angina or a related condition (e.g., elevated BP or supraventricular tachycardia) or if BBs are poorly tolerated or contraindicated.[75,77-79] In the setting of unstable angina and concomitant BB use, long-acting dihydropyridine CCBs may be preferable to nondihydropyridine CCBs due to the possibility of excessive bradycardia or heart block associated with the latter agents. Short-acting dihydropyridine CCBs should be avoided in patients with acute MI, pulmonary edema, or LV dysfunction. Compared with patients treated with other antihypertensive agents (diuretics and BBs), hypertensive patients treated with short-acting CCBs have a 60% higher risk of MI.[80]

Randomized trials of nondihydropyridine CCBs in patients with acute MI have shown benefit in preventing CVD events but no significant influence on overall mortality. Verapamil use was associated with a 20% reduction in first major events due to CV causes (death and reinfarction) in the Danish Verapamil Infarction Trial II[81] and a significant 19% decrease in reinfarction in a meta-analysis of 28 randomized trials in approximately 19,000 post-MI patients.[82] However, in these and other trials, no significant decrease in mortality has been shown with verapamil treatment. A large trial (the Multicenter Diltiazem Postinfarction Trial [MDPIT]) demonstrated no reduction in mortality or reinfarction with diltiazem treatment.[83] In patients with depressed LV function or pulmonary edema, or both, a 41% increase in CVD events (death from a cardiac cause and nonfatal MI) was noted in persons receiving diltiazem. **Thus CCBs do not reduce mortality in the setting of AMI and are not recommended except in situations where BBs are poorly tolerated or inadequate to control concomitant conditions (e.g., BP, angina, supraventricular tachycardia)**.[75]

ACEIs are indicated in all patients with acute MI who can tolerate them. In a hemodynamically (SBP $\geq$ 90 to 100 mm Hg) stable patient post-MI, an oral ACEI should be initiated, generally within 24 hours of onset of the event, particularly if the MI is anterior and associated with depressed LV function (LVEF < 40%) or HF, or both.[75] The patient's creatinine and electrolytes should be measured before initiation of ACEI therapy and periodically until the highest tolerated dose of the agent has been given and the patient has shown stable renal function. Although guidelines do not specify any particular level of serum creatinine (or estimated glomerular filtration rate) above which ACEIs or ARBs should not be administered, the outcome trials on which they are based have generally excluded patients with a serum creatinine $\geq$ 2.5 mg/dL. Accordingly, evidence of benefit in this patient group is lacking. As in patients with renal disease, modest (<30%) increases in serum creatinine are seen frequently in patients with acute MI following initiation of ACEI or ARB treatment and should not be a cause for concern (see Chapter 35). Greater increases may signify excessive volume depletion, worsening HF, or bilateral renal artery stenosis, and the patient should be evaluated carefully for these conditions. Hyperkalemia ($K^+ \geq 5.0$ mEq/L) associated with ACEI use can sometimes be dealt with by adjusting diuretic doses and stopping K^+ supplements and other agents known to increase K^+ (e.g., NSAIDS) and modifying diet. Use of ACEIs after acute MI has led to a significant reduction in mortality. ACEI therapy is particularly beneficial in patients classified as high risk (Killip class 2 or 3, HR $\geq$ 100 bpm). Current guidelines recommend that ACEI be initiated routinely after acute MI and continued for an indefinite period.[75]

ARBs are indicated for patients with acute MI who are intolerant of ACEIs and have clinical or radiological signs of HF or LVEF < 0.40. Further, ARBs are an accepted alternative to ACEIs in this patient group even if among persons who can tolerate ACEIs.[75] Valsartan and candesartan have established efficacy for this recommendation. ACE-ARB combinations can be considered in the long-term management of these patients if symptomatic HF and LVEF < 0.40 persist or if BP is uncontrolled, or both. Further, aldosterone blockade is recommended for post-MI patients without significant renal dysfunction (Cr $\leq$ 2.5 mg/dL in men, $\leq$ 2.0 mg/DL in women) or hyperkalemia ($K^+ \geq 5.0$ mEq/L) who are receiving therapeutic doses of an ACEI and have an LVEF $\leq$ 0.40 and either

Table 34–3 Common Adverse Effects and Precautions Regarding Use of Antihypertensive Drugs

Drug Class	Adverse Effects	Precautions and Special Conditions
β-Blockers	Bradycardia, negative inotropic effect, fatigue, insomnia, bizarre dreams, sexual dysfunction, hypertriglyceridemia, decreased HDL cholesterol, may mask hypoglycemic symptoms, may worsen symptoms of PAOD, may suppress exercise tolerance, rebound hypertension or angina, or both, can occur with abrupt withdrawal	Should not be used in patients with asthma, chronic obstructive pulmonary disease, second- or third-degree heart block, particularly when nondihydropyridine CCBs are administered concomitantly, and sick sinus syndrome: use in HF requires careful titration, special precautions: use with caution in patients with diabetes and peripheral vascular disease: sudden withdrawal of these drugs may be hazardous
ACE inhibitors	Cough, much less common are angioedema, rash, hyperkalemia	Can cause renal failure in patients with severe HF, who are overdiuresed, hemodynamically unstable after AMI, or who have bilateral renal artery stenosis: creatinine and electrolytes should be measured before initiation of therapy and periodically until dose titration is complete: contraindicated in pregnancy because of possible teratogenic effects: neutropenia may occur in patients with autoimmune collagen disorders
Angiotensin receptor blockers	Hyperkalemia, angioedema (rare)	May share adverse effects of ACE inhibitors other than cough: contraindicated in pregnancy because of possible teratogenic effects: more clinical experience in high-risk patients is necessary for full assessment of risk
Aldosterone receptor blockers	Hyperkalemia, gynecomastia, mastodynia, sexual dysfunction	Potassium levels must be monitored, particularly in patients treated with ACE inhibitiors, angiotensin receptor blockers, potassium-sparing diuretics, or potassium supplementation
Calcium channel blockers Dihydropyridines	Ankle edema, flushing, headache, gingival hypertrophy (uncommon), increase in heart rate may occur	Short-acting dihydropyridines should be avoided in patients with AMI, pulmonary edema, or left ventricular dysfunction: long-acting dihydropyridines in AMI should be reserved for situations where β-blockers or other agents, or both, are inadequate to control concomitant conditions (e.g., blood pressure, angina, severe ventricular tachycardia): not useful in HF
Nondihydro-pyridines	Constipation, first-degree heart block, bradycardia, worsening of systolic dysfunction	Use with caution in patients with HF, heart block, sick sinus syndrome, bradycardia, particularly when β-blockers are administered concomitantly; in AMI, should be reserved for situations where β-blockers or other agents, or both, are inadequate to control concomitant conditions

symptomatic HF or diabetes. BP control with a combination of lifestyle modification and antihypertensive drugs is critical for the post-MI patient, and guidelines suggest an aggressive target goal of 120/80 mm Hg.

HEART FAILURE

HF is the only form of CVD that is increasing in incidence, prevalence, and overall mortality. Importantly, 40% to 50% of patients with symptoms of HF may have preserved systolic function. These patients are more likely to have hypertension, LVH, and isolated diastolic dysfunction and are more likely to be women.[8,84] Data from the Framingham Heart Study show that in 91% of new cases, HTN antedated the development of HF.[85] In a multivariate analysis, HTN was associated with 39% of HF cases in men and 59% in women, with a twofold to threefold increased risk for HF overall. Survival rates for HF are dismal: 25% in men and 38% in women at 5 years. As HTN detection, treatment, and control have improved, prior MI has become increasingly important as a risk factor for HF. According to some reports, 60% to 70% of HF patients have had a prior MI and have developed symptoms due to LV remodeling.[86]

The path from HTN to HF involves the interplay of HTN and MI, as well as LVH and ventricular remodeling, and is mediated by a complex array of neurohormonal and mechanical changes over time (Fig. 34–11A). Norepinephrine, angiotensin II, endothelin, aldosterone, and tumor necrosis factor-alpha (TNF-α) contribute to the progression of HF and provide targets for pharmacologic therapy.[87-89] Therapy in the acute setting includes diuretics with or without inotropes and vasodilators. These agents decrease preload and help relieve symptoms related to volume overload (see Fig. 34–11B). The strategies of antagonizing salt and fluid retention or improving hemodynamics (increasing cardiac output, reducing systemic vascular resistance), or both, do not prevent the progression of HF or improve life expectancy for patients with

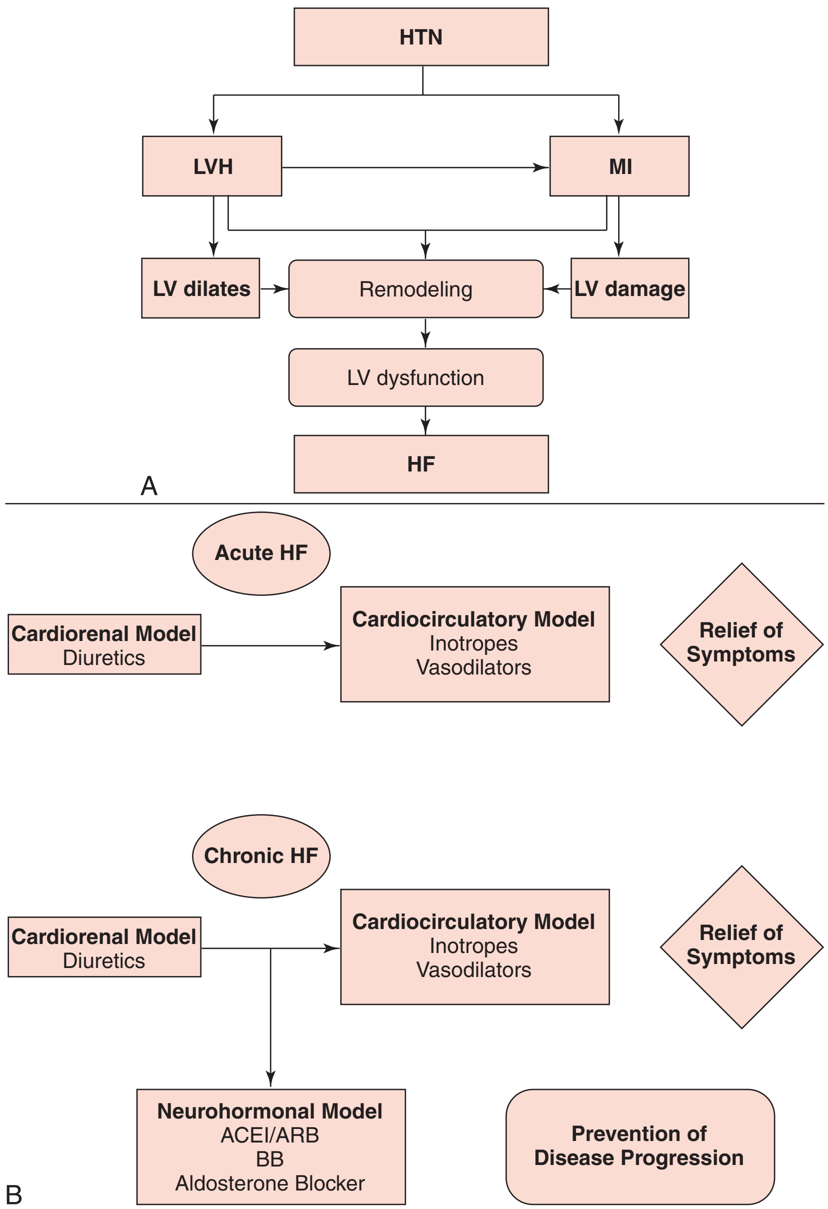
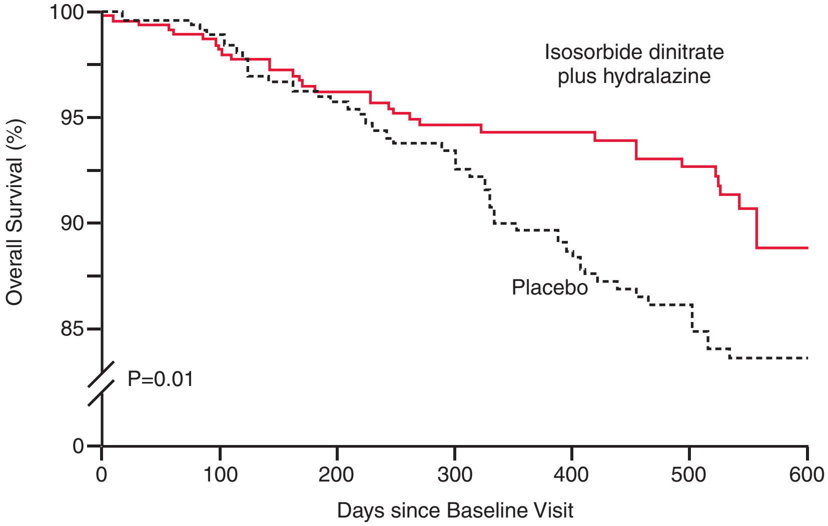


Figure 34–11 **A,** Schematic depiction of various steps responsible for the progression from hypertension to congestive heart failure. (Reproduced with permission from Deedwania PC: The progression from hypertension to heart failure. Am J Hypertens 1997;10:280S-8S.) **B,** Treatment of acute heart failure or cardiac decompensation, or both. Combinatorial use of the cardiorenal (diuretics) and cardiocirculatory models (vasodilators and inotropes) represents an effective strategy for treating patient symptoms related to excessive volume overload. Treatment of chronic heart failure. Neurohormonal antagonists (ACE inhibitors, ARBs and aldosterone blockers and β-blockers) should be used to prevent disease progression in heart failure. Moreover, combinatorial use of diuretics (cardiorenal model) is indicated in order to treat symptoms related to excessive volume overload. (Reprinted from Mann DL: Mechanisms and models in heart failure. Circulation 1999;100:999-1008.)

moderate to severe disease but are necessary for symptom relief in patients with acute or chronic HF.

HF is a "compelling indication" for the use of ACEIs in the patient with HTN.[8] Abundant evidence exists to justify their use with all stages of HF (see Table 34–1).[90] Most importantly, elevated levels of BP, especially SBP, are major risk factors for the development of HF,[85,91] and long-term treatment of HTN has been shown to effectively reduce the risk of HF.[92,93] Optimal BP control decreases the risk of new HF by approximately 50%.[94] In addition, ACEIs decrease both preload and afterload and have favorable effects on LV remodeling and endothelial function.[95-99] Thus ACEI therapy reduces morbidity and mortality in patients with established HF.[100,101] These outcome benefits likely relate to their anti-thrombotic and prothrombolytic effects and their favorable effects on oxidative stress in the vasculature and the myocardium, as well as their beneficial effects on LV and vascular remodeling. The benefits of ACEI therapy in HF are independent of age, sex, and the use of other pharmacologic agents, such as diuretics, aspirin, and BBs. Importantly, major clinical trials in HF or LV dysfunction including SOLVD, AIRE, SMILE, TRACE, and CONSENSUS have reported sustained post-trial benefits with ACEIs.[102-105] The sustained and incremental post-trial benefit in these studies is thought to be related to the favorable impact of ACEI therapy on LV remodeling in patients with LV dysfunction and myocardial damage.

An analysis of pooled data from the SOLVD trial has shown that there appears to be less benefit of ACEI therapy in black HF patients compared with white HF patients.[106] The combination of hydralazine and nitrates, when added to standard therapy, has been shown to reduce mortality significantly in African-American patients with HF when compared with placebo (Fig. 34–12).[107] This combination has received FDA approval for the treatment of HF in African-American patients, making it the first race-specific CV pharmacologic therapy. However, on the basis of the large body of evidence available, it is recommended that all



No. at Risk							
Placebo	532	466	401	340	285	232	24
Isosorbide dinitrate plus hydralazine	518	463	407	359	313	251	13

Figure 34–12 Kaplan-Meier survival analysis shows a 43% increase in survival in African-American patients with HF treated with isosorbide dinitrate + hydralazine compared with placebo. (Reproduced from Taylor AL, Ziesche S, Yancy C, et al: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57.)

patients with HF, including African-Americans, be placed on ACEI therapy unless contraindicated.

ARBs and mineralocorticoid (aldosterone) receptor antagonists provide alternative mechanisms for disruption of the RAAS. These agents have been tested as alternatives or additions, or both, to ACEI therapy in HF.[60,62,108-114] In general, these trials have shown benefit with ARB treatment, particularly in ACEI-intolerant patients. The mineralocorticoid receptor antagonists spironolactone and eplerenone are recommended for use in HF (usually in combination with a diuretic) as a result of the reduced morbidity and mortality shown in the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS).[113,114] The benefit of these agents in HF is believed to be related to blockade of mineralocorticoid receptors in the heart and vasculature, with related cardioprotective and vasoprotective effects rather than their diuretic actions. Hyperkalemia is a risk with aldosterone antagonists, even at low doses (especially because most patients are taking ACEIs or ARBs), but its incidence can be reduced by limiting therapy to patients with serum creatinine < 2.5 mg/dL and monitoring serum potassium carefully.

BBs (both nonselective and β-1 selective) appear to benefit patients with HF and HTN because of their ability to block sympathetic activation, which is believed to play an important part in the progression of HF, as well as the pathogenesis of HTN. In addition, the nonselective BB carvedilol has both α- and β-adrenergic blocking effects, which help to reduce cardiac norepinephrine levels,[115] as well as antioxidant effects, which may protect against cardiac myocyte loss. The morbidity and mortality benefits of BBs in HF have been shown in a number of large trials, as reviewed in detail in Chapter 14.[116-125]

BP targets in HF have not been firmly established, but lowering SBP is almost uniformly beneficial.[8] In most successful trials, SBPs were lowered to the range of 110 to 130 mm Hg. One trial demonstrated benefits of BBs in patients with SBP > 85 mm Hg, suggesting that low BPs (e.g., SBP < 100 mm Hg) may be desirable in some HF patients.[122]

Unlike the ACEIs, ARBs, mineralocorticoid receptor antagonists, BBs, and diuretics, the CCBs have not been shown to provide benefit to patients with HF.[126-128] **On the basis of these findings, CCB use in HF is not recommended.** Further, in randomized controlled outcome trials of antihypertensive treatment, CCBs have been shown to be less effective than other drug classes in preventing HF.[5,8,53] **Similarly, α-adrenergic blockers have not been shown to be effective in preventing HF in patients with HTN and are not recommended for that indication.[129]**

HYPERTENSION AND CEREBROVASCULAR DISEASE

HTN is the most powerful risk factor, after age, for stroke. Elevated SBP, DBP, and a widened PP are all associated with higher stroke rates.[130] Data from the Framingham Heart Study show an age-adjusted relative risk of stroke in persons with HTN of 3.1 for men and 2.9 for women.[131] Randomized controlled trials have shown that all of the major classes of antihypertensive agents including diuretics, BBs, CCBs, ACEIs, and ARBs are effective in preventing stroke compared with placebo or, in the case of ARBs, an active comparator.

A prospectively designed overview of data from 29 randomized controlled trials with 162,344 participants revealed that weighted mean SBP differences between randomized groups are directly associated with differences in risk of stroke.[5] In this analysis, CCB-based regimens tended to be more effective than either ACEI-based (12% reduction) or diuretic-BB-based regimens (7% reduction) in preventing this outcome, although none of these differences achieved statistical significance. Greater risk reductions were seen with regimens targeting lower BP goals (23% reduction) independent of

drug class. Subsequent meta-analyses have concluded that CCBs decrease the risk of stroke more effectively than other treatments in patients with essential hypertension and that the benefit may not be completely explained by a better BP response.[132,133]

Subgroup analyses of trials with dihydropyridine and nondihydropyridine CCBs revealed significant reduction in stroke risk with dihydropyridines but not with nondihydropyridines compared with control active treatment regimens.[132] Meta-regression analysis showed that CCBs were superior to ACEIs for prevention of stroke and that the difference could not be accounted for by BP differences.[133] Posthoc analyses from the ALLHAT trial confirmed the superiority of dihydropyridine CCB compared with ACEI treatment for stroke prevention, particularly in blacks (51% risk reduction) and women (45% risk reduction); diuretic-based treatment decreased stroke risk by 40% compared with ACEI treatment in blacks.[53,134] Time-dependent BP adjustment did not significantly alter differences in outcome. The ASCOT trial, not included in the meta-analysis because of its later publication date, showed a significant 25% reduction in stroke with dihydropyridine CCB-based compared with BB-based treatment, an effect that could not be accounted for by BP differences but may be related to selective reduction of central arterial pressure with CCBs compared with BBs, as demonstrated in the CAFÉ substudy.[21,29]

Active comparator trials of ARB-based versus BB- or conventional therapy–based treatment have provided the strongest evidence for BP independent benefits of any drug class in stroke prevention.[65,135-138] The LIFE trial demonstrated a 25% reduction in stroke with ARB (losartan)-based compared with BB (atenolol)-based treatment despite minimal differences in achieved BPs in more than 9000 patients with hypertension and LVH by ECG.[65,135,136] Mechanisms that have been adduced to account for this benefit of losartan include favorable effects on endothelial function, reflected in selective reductions in microalbuminuria;[139] favorable effects on vascular remodeling/atherosclerosis, reflected in reduced carotid intima/media thickness; reductions in LVH and left atrial size[140,141]; uricosuria[142]; and reductions in new onset atrial fibrillation, as well as in stroke incidence in patients with established atrial fibrillation.[136,143] Further study is necessary to evaluate the generalizability of these findings to patients without LVH, to other ARBs, and to different comparator regimens.

The Study on Cognition and Prognosis in the Elderly (SCOPE) trial compared candesartan-based with conventional antihypertensive therapy (diuretic, BB, CCB, ACEI) in 4964 elderly patients with mild to moderate HTN.[137,138] The candesartan group experienced a significant 28% reduction in nonfatal stroke, as well as a trend toward significant reduction in all stroke of 23% when compared with the control group. In a substudy of SCOPE, elderly patients with ISH experienced a robust 40% reduction with candesartan treatment compared with conventional therapy.[138]

Two major outcome trials have tested various classes of antihypertensive drugs in the secondary prevention of stroke.[144,145] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) compared ACEI therapy with and without a diuretic to placebo in more than 6100 patients with a prior stroke or transient ischemic attack.[144] The combination of ACEI and diuretic led to a reduction in BP of 12/5 mm Hg and a reduction in risk of stroke of 43%. No significant difference in the risk of recurrent stroke was seen in the perindopril-only group, which showed a 5 mm Hg reduction in SBP. Interestingly, the benefits of ACEI + diuretic treatment were seen in both normotensive and hypertensive persons and in those with and without diabetes.[146] Both ischemic and hemorrhagic stroke were prevented with this treatment regimen.

The MOrbidity and mortality after Stroke-Eprosartan compared with nitrendipine in Secondary prevention (MOSES) study compared ARB-based and dihydropyridine CCB-based treatment in prevention of secondary stroke.[145] Despite equal BP reductions in both arms, the ARB arm produced significant reductions (21%) in the primary endpoint (total mortality, total CV, and cerebrovascular events) and in stroke (25%) and a trend toward reduction in CV events. Results of the MOSES trial reaffirm the effectiveness of the ARB class of antihypertensive drugs in stroke prevention and the suggestion that these agents may have benefits beyond BP reduction.

HYPERTENSION AND PERIPHERAL ARTERIAL DISEASE

HTN, DM, and smoking are major risk factors for PAD. Symptomatic PAD is associated with a greatly increased risk of death from CVD, in part because diffuse atherosclerosis, CHD, and renovascular disease frequently coexist in these patients.[8] Therefore the threshold for screening for these related CV disorders in patients with PAD should be low (see Chapter 33). In particular, renovascular hypertension should be strongly considered in this population if BP is uncontrolled and if ACEI or ARB treatment is being considered.

Antihypertensive drug treatment is ineffective in relieving symptoms of PAD. Vasodilator agents, such as ACEIs, CCBs, α-adrenergic blockers, and direct vasodilators, have not been shown to improve walking distance or symptoms of claudication in patients with PAD.[147] Whether this is due to the inability of diseased vessels to dilate further because they are maximally dilated during exercise, to a "steal" phenomenon in which blood flow increases in nondiseased vascular beds at the expense of diseased beds, or to the possibility that BP reduction distal to occluded areas of diseased arteries decreases forward blood flow due to a loss of "driving" pressure is unknown. BBs may precipitate peripheral vasoconstriction and increase the frequency of intermittent claudication in patients with PAD.[148-150] However, studies have shown that BBs do not decrease walking distance or calf blood flow in these patients.[148] Thus BBs can be used in PAD patients, particularly for the treatment of concomitant conditions (e.g., CHD or HF.[8,151] ACEIs are also recommended for symptomatic patients with lower extremity PAD to reduce the risk of adverse CVD events.[151]

PAD has begun to emerge as a prespecified endpoint in controlled outcome trials of antihypertensive therapy. In the United Kingdom Prospective Diabetes Study Group (UKPDS) trial, tight BP control (mean achieved BP = 144/82 mm Hg vs. 154/87 in the less tight control group) in patients with HTN and DM led to significant reductions in risk of death, complications related to DM, and stroke and microvascular disease but no significant decrease in PAD risk.[152] Within the tight BP

control group in UKPDS, patients were further randomized to ACEI (captopril) or BB (atenolol) treatment.[153] Although the ACEI and BB were equally effective in reducing the risk of macrovascular endpoints, including PAD, this relatively small study (≈400 participants/treatment group) lacked the power to detect small but possibly clinically important differences in outcomes. Importantly, compliance with assigned treatments was significantly lower in the BB group, in part due to an increased incidence of intermittent claudication or cold feet.

The larger ASCOT trial, in which PAD was a tertiary endpoint, showed a statistically significant 35% excess of PAD with the atenolol-based compared with the amlodipine-based regimen.[29] This finding, coupled with the excess of peripheral coldness noted as an adverse event in the atenolol-based group, suggests that a BB may not be a desirable first drug for prevention of PAD in patients with HTN and other CVD risk factors. In contrast, results of the ALLHAT trial showed that risk of developing hospitalized or treated PAD did not differ significantly among diuretic (chlorthalidone)–, CCB (amlodipine)–, and ACEI (lisinopril)–based treatment groups.[53]

Because no class of antihypertensive medications offers particular benefit to the patient with PAD, treatment choices should be made on the basis of concomitant conditions (CHD, DM, HF).[8,151] ACEIs are recommended to reduce the risk of adverse CVD events, as in other high-risk patient populations. Evidence for this recommendation comes from the HOPE trial, which showed that, in patients with symptomatic PAD, the ACEI ramipril reduced the risk of MI, stroke, or vascular death by approximately 25%, an effect size comparable to that achieved in the study population as a whole.[27] BBs are not contraindicated in PAD but have disadvantages in terms of symptomatic adverse events. Renal artery stenosis should be ruled out in this high-risk population before initiation of ACEI or ARB treatment. If the agents mentioned earlier fail to control BP or are poorly tolerated, or both, or if the patient has Raynaud's phenomenon, CCBs can be used.

Lifestyle modification plays a particularly important role in the management of patients with HTN and PAD.[8] A structured walking program has been shown to increase the pain-free and maximum walking distances in patients with intermittent claudication.[154] Smoking cessation may be the most important factor in whether PAD progresses. Accordingly, patients should be encouraged and assisted to stop smoking. Lipid abnormalities should be controlled using lifestyle modification and drugs as appropriate. Coexisting glucose intolerance or insulin resistance calls for increased exercise and weight reduction, and aggressive management of diabetes is indicated. In addition, antiplatelet therapy is critical in these patients to reduce the risk of limb ischemia.[151]

HYPERTENSION AND ATRIAL FIBRILLATION

ACEIs and ARBs can prevent the onset and reduce the recurrence of AF.[155] Mechanisms responsible may include beneficial structural remodeling of the atria and LV, reductions in atrial interstitial fibrosis and angiotensin II–induced norepinephrine release, and possibly direct antiarrhythmic effects.[156] In a subanalysis from the LIFE study, after 5 years of follow-up, 150 patients in the losartan arm developed new-onset AF compared with 221 in the atenolol arm, a significant reduction.[136] In a study of 79 patients treated with irbesartan (150 to 300 mg/d) in combination with amiodarone (400 mg/d) versus 75 patients treated with amiodarone alone (400 mg/d), 80% of patients in the combination arm remained in sinus rhythm approximately 9 months after successful cardioversion from AF compared with 56% of those treated with amiodarone monotherapy.[157] A meta-analysis of 11 studies with 56,308 participants showed a 28% reduction in relative risk of AF in those treated with ACEIs or ARBs.[155] The greatest effect was demonstrated in HF patients, who experienced a 44% relative risk reduction. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-I) trial will randomize 14,000 AF patients with and without HTN to an ARB or placebo. Three years of follow-up will occur, and the primary endpoint will be a composite of stroke, MI, or vascular death. The irbesartan arm of this trial will provide more conclusive data on the effects of ARBs on AF.

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Chapter 35

Treatment of Hypertension in Patients with Renal Disease

Nitin Khosla and George L. Bakris

CHAPTER CONTENTS

INTRODUCTION

A survey of the National Health and Nutrition Examination Survey (NHANES) database estimates that 50 million Americans have high blood pressure.[1] The degree and duration of elevation in either systolic or diastolic blood pressure (BP) substantially increases the risk of developing a cardiovascular event or renal disease.[2] In fact, for every increment of 20 mm Hg in systolic BP and 10 mm Hg in diastolic blood pressure over 115/75 mm Hg, the risk for a cardiovascular event doubles.[3] People with kidney disease are at a particularly high risk of developing cardiovascular complications from elevated blood pressures.[4,5] This is especially true among those with proteinuria >300 mg/day.[6,7] Current guidelines suggest that lowering blood pressure to <130/80 mm Hg in this cohort can prevent or delay the onset of kidney failure.[2,8]

The results of any clinical trial that evaluates antihypertensive treatment on kidney disease progression must be considered in the context of the following factors: (a) goal blood pressure achieved and time to achieve goal; (b) stage of the kidney disease at the inception of a trial; and (c) presence or absence of macroalbuminuria (proteinuria, i.e., >300 mg/d albumin in urine). These factors are important because earlier intervention is much more likely to arrest kidney disease progression than later intervention that will only slow disease progression. This is illustrated by the results of two different renal outcome trials with widely divergent baseline glomerular filtration rates (GFR) and levels of proteinuria. In The Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the average GFR was more than 80 mL/min at the start of the trial, whereas in other diabetes trials the GFR is generally less than 50 mL/min at baseline.[9] Early and aggressive BP lowering (i.e., <130/80 mm Hg) in the ABCD trial was associated with GFR decline being slowed to rates seen in people with normal kidney function. Conversely, in other trials of more advanced kidney disease, GFR loss occurred at a rate of 2 to 7 mL/min/yr.[8,10] Thus, results of clinical trials in patients with advanced renal disease should not be extrapolated to patients with early disease because rates of decline in renal function are not comparable unless baselines are similar.

This chapter deals exclusively with the management of hypertension in chronic renal disease. Management of this condition focuses on agents that not only lower BP but also reduce microalbuminuria (MA) or macroalbuminuria (proteinuria), or both. The presence of MA is an independent risk marker associated with a higher incidence of cardiovascular events in all subjects independent of kidney disease or diabetes.[11-14]

MA is defined as a protein excretion of 30 to 299 mg/d or 20 to 200 mcg/min present on two different occasions. Protein excretion >300 mg/d or >200 mcg/min represents overt proteinuria.[15] Urinary protein excretion is best assessed by the albumin-to-creatinine (mg/g) ratio in a spot urine specimen. A guide to the evaluation of MA is presented in Figure 35–1.[15] The overall treatment goal in patients with hypertension and any level of albuminuria is to achieve target BP goal using agents that also reduce MA or proteinuria. The reason for this is that blood pressure lowering alone does not totally account for the magnitude of albuminuria reduction. Reduction in macroalbuminuria (proteinuria) has been shown in five outcome trials to delay markedly the need for dialysis in people with advanced proteinuric kidney disease, Table 35–1. This benefit on kidney disease progression could not be explained by blood pressure lowering alone in these trials.[16-19] In three of these studies a reduction in proteinuria of more than 35% resulted in a 39% to 72% risk reduction for dialysis at 3 to 5 years.[17-19] The data on cardiovascular benefit from MA reduction are less clear; however, data from the LIFE trial indicated a benefit of early MA reduction on cardiovascular events extending out to 5 years.[20]

NONDIABETIC RENAL PARENCHYMAL DISEASE

The incidence of renal insufficiency progressively increases with every 10 mm Hg increment in systolic pressure.[21] End-stage renal disease (ESRD) resulting from causes unrelated to diabetes is most often attributed to hypertensive nephrosclerosis. Pathologically, this is represented by hyalinization and

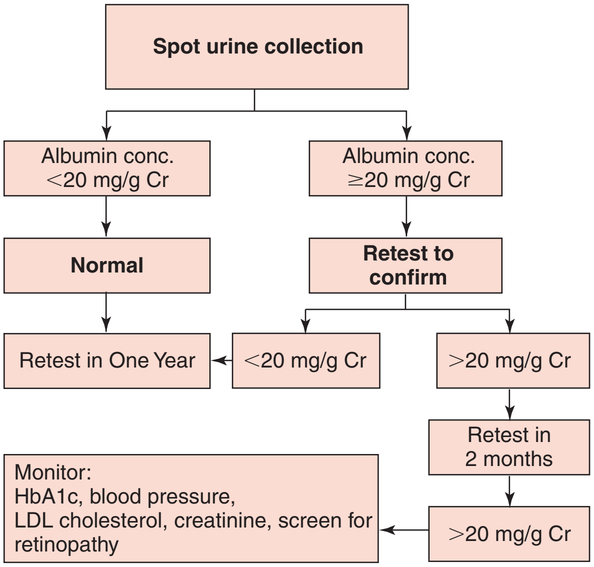

Figure 35–1 Evaluation and work-up of microalbuminuria. (Modified from Keane WF, Eknoyan G: Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): A position paper of the National Kidney Foundation. Am J Kidney Dis 33:1004-10, 1999.)

sclerosis of the walls of the afferent arterioles. The other major finding that heralds the development of hypertensive renal disease is the development of MA, which is felt to be both a marker of impaired endothelial responsiveness and a likely factor in the initiation and progression of tubulointerstitial renal injury.[22,23]

Some of the earlier trials that evaluated progression of kidney disease resulting from causes other than diabetes include The Ramipril Efficacy in Nephropathy (REIN), Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI), and Modification of Dietary Protein in Renal Disease (MDRD) trials, as well as other smaller trials. These trials all demonstrate the importance of lowering BP to slow progression of nondiabetic kidney disease.[24,25]

Although BP reduction is important, consideration must be given to agents that preferentially reduce albuminuria because that is an independent factor affecting progression of kidney disease. This is further demonstrated by a meta-analysis of clinical trials in patients with nondiabetic renal disease, which found that the use of angiotensin-converting enzyme (ACE) inhibitors delays the progression of renal disease, an effect shown to relate to the magnitude of proteinuria reduction, as well as BP.[26] Perhaps the most compelling data come from the substudy of the COOPERATE trial. In this trial of IgA nephropathic patients with an average GFR of <50 mL/min and 2.3 g of proteinuria, using the combination of an ACE inhibitor with an angiotensin receptor blocker (ARB) in the same doses used individually resulted in greater slowing of kidney disease progression, an effect that could not be explained by differences in 24-hour ambulatory blood pressure data (Fig. 35–2).[19] It should be noted that use of an ACE inhibitor with ARB at high doses of each does *not* offer a significant BP advantage but rather has only been shown to benefit outcome in people with advanced nephropathic disease and not cardiovascular disease, such as post myocardial infarction or heart failure.[27,28]

Table 35–1 Clinical Renal Outcomes Trials in the Context of the Primary Outcome in Relation to Changes Observed in Proteinuria*

Increased Time to Dialysis (30-35% Proteinuria Reduction)	No Change in Time to Dialysis (No Proteinuria Reduction)
Captopril Trial[89]	IDNT (DHPCCB arm)[60]
AASK Trial[90]	AASK (DHPCCB arm)[90]
RENAAL[59]	
IDNT[60]	
COOPERATE[61]	

*In the RENAAL, COOPERATE, and AASK trials these results were independent of changes in glomerular filtration rate (GFR) or baseline GFR and achieved blood pressure reduction.

DIABETES AND CHRONIC RENAL DISEASE

In patients with type 1 diabetes, the onset of hypertension closely correlates with the development of renal disease. The incidence of hypertension rises from 5% at 10 years to 33% at 20 years and 70% at 40 years, but hypertension is present in only 2% to 3% of those without clinically evident renal involvement. Such patients may have underlying essential hypertension rather than elevated blood pressure related to their diabetes. This is in contrast to patients with type 2 diabetes.

Both hypertension and an abnormal circadian BP profile are strongly correlated with the presence of albuminuria and are powerful predictors of cardiovascular or renal events.[29] A retrospective study collected ambulatory blood pressure monitoring in a clinic setting in 75 patients with diabetes and followed them for a median of 42 months. Over time, dippers had a lower mortality than nondippers, with 8% deaths in the cohort of dippers and 26% deaths in the cohort of nondippers. They also noted that age, duration of diabetes, and baseline renal function were independent risk factors for mortality in nondippers. They also noted a fourfold increase in mortality in those who had normal kidney function and converted to nondipping BP status. This study suggests a role for ambulatory BP monitoring in day-to-day clinical practice to select patients with nephropathy who are at greatest risk and to focus aggressively on treatments that may alter outcome.[30]

The risk of target organ damage resulting from hypertension is highest in blacks with diabetes, who are also at much greater risk for renal failure from diabetic nephropathy. Early studies showed an increased risk of renal disease in certain ethnic groups related to ACEI/D polymorphisms (which could increase ACE levels) interacting with angiotensinogen M 235T polymorphisms (which could increase angiotensinogen levels). Moreover, those who do not have clinically evident diabetes but with a genetic predisposition to diabetic nephropathy have higher BP levels than those with no family

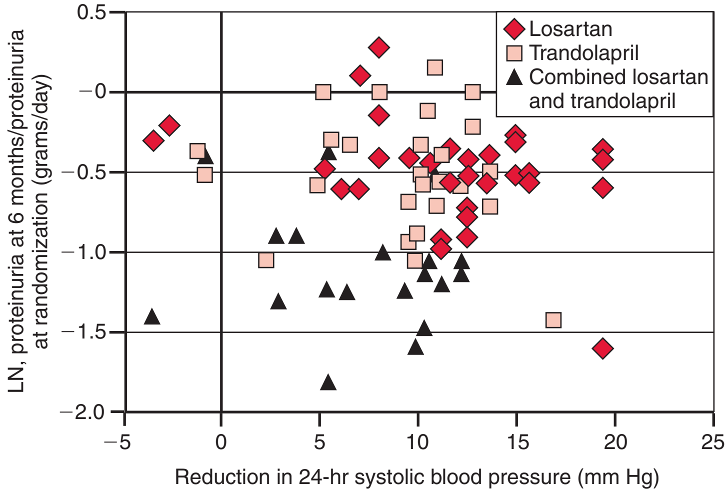

Figure 35–2 The change in ambulatory blood pressure and proteinuria following 6 months of treatment of advanced nondiabetic kidney disease predicted outcome at 3 years. Note that the dose of losartan was 100 mg/d, of trandolapril was 3 mg/d, and the combination was the same doses combined. (Modified from Nakao N, Seno H, Kasuga H, et al: Effects of combination treatment with losartan and trandolapril on office and ambulatory blood pressures in nondiabetic renal disease: A COOPERATE-ABP substudy. Am J Nephrol 2004;24:543-8.

history of the disease. These observations have been verified in a meta-analysis of more than 14,000 patients and emphasize the especially high risk in the Asian population.[31] The actual genetic link to predicting nephropathy in diabetes is inconclusive. A review of all such factors including studies of genes related to inflammatory markers has not revealed a clear answer.[32] Ongoing studies may provide an answer within the next decade.

The strongest risk factors for nephropathy development and progression in those with diabetes are presence of hypertension and poor glycemic control and development of macroalbuminuria (proteinuria).[33,34] Detection of MA is a predictor of overall cardiovascular morbidity and does not predict nephropathy development unless it increases to macroalbuminuria or proteinuria.[35,36] Development of proteinuria despite adequate BP control is a clue that renal disease is present and progressing. The presence of proteinuria of >2.5 g per day is an uncommon consequence of hypertension alone and should prompt a renal biopsy to determine the etiology of renal disease or at least an evaluation for occult diabetes. More than 40% of patients with diabetes develop the syndrome of diabetic nephropathy defined by increases in arterial pressure, persistent proteinuria, and decline in GFR. The presence of nephropathy is associated with increased morbidity and mortality rates because of both increased cardiovascular events and end-stage renal failure.[37]

Patients with diabetes and macroalbuminuria are 20 times more likely to die of cardiovascular disease than those without albuminuria. Hence treatment is aimed at both lowering arterial pressure to a stated goal and reducing proteinuria by at least 30% to 50% from baseline.[8,37,38] The person with diabetes should be started on antihypertensive medications even if the BP is in the high-normal range (>130/80 mm Hg) because of the greatly heightened cardiovascular and renal risks.[2,8]

THERAPEUTIC APPROACHES TO HYPERTENSION IN KIDNEY DISEASE

Lifestyle approaches to treating blood pressure in those with early kidney disease are summarized in Table 35–2.[2,8] Specific attention is given to sodium intake because it contributes relatively more to increasing BP than do other lifestyle factors.

Table 35–2 Summary of Lifestyle Modifications[2]

Modification	Approximate SBP Reduction (Range)
Weight reduction	5-20 mm Hg/10 kg weight loss
Adopt DASH eating plan	8-14 mm Hg
Dietary sodium reduction	2-8 mm Hg
Physical activity	4-9 mm Hg
Moderation of alcohol consumption	2-4 mm Hg

DASH, Dietary Approaches to Stop Hypertension.
Modified from the JNC 7-SBP systolic blood pressure.

Sodium Restriction

Sodium retention is a major pathophysiological mechanism of hypertension development in chronic renal disease. Sodium retention is also a major contributor to BP elevation in the presence of insulin resistance because insulin increases proximal tubular sodium reabsorption.[39,40] Hence, those who are obese or have diabetes are relatively volume expanded.[41] Therefore, limitation of daily sodium intake to 2 to 4 g/d is a logical initial therapeutic approach. Salt restriction is also important because excessive dietary sodium intake (i.e., >6 g/d) attenuates the effects of ACE inhibitors and ARBs on proteinuria reduction.[42] Further, because blacks with essential hypertension demonstrate greater angiographic and histological evidence of arteriolar nephrosclerosis than whites and because both normotensive and hypertensive blacks excrete a lower sodium load than their white counterparts, sodium restriction is particularly important in blacks with essential hypertension.[42] The importance of this difference in renal sodium handling is borne out by the results of the DASH diet, in which hypertensive black females had a 6 mm Hg greater reduction in BP compared with hypertensive white females on this low-sodium, high-potassium diet.[43] Note that this diet can be given to those with up to early stage 3 nephropathy (GFR>30<59). After that, the high potassium intake should be reduced.

This sluggish response to sodium loading in the black population is associated with a higher prevalence of salt-sensitive hypertension and lower plasma renin activity than in white

hypertensive patients. Lastly, sodium restriction clearly contributes to the maintenance of BP reductions in elderly patients with established hypertension.[44]

Pharmacologic Treatment

The guidelines of both the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the National Kidney Foundation (NKF) state that all patients with kidney disease should receive either an ACE inhibitor or ARB along with lifestyle modifications and dietary changes if BP is >140 mm Hg.[2,10] Figure 35–3 illustrates an updated, integrated approach to achieve BP goal amalgamating the JNC 7, NKF, and American Diabetes Association (ADA) guidelines for those with kidney disease or diabetes, or both.[2,8,45,46]

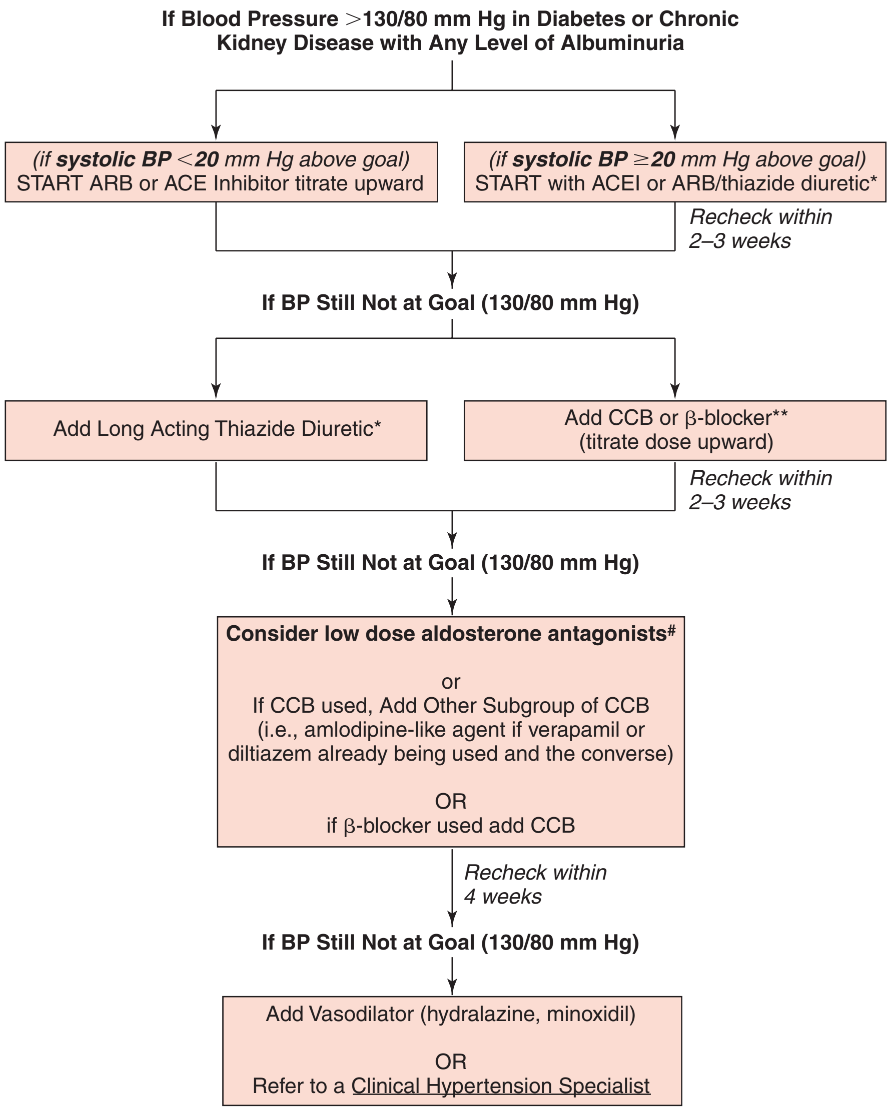

Figure 35–3 An approach to lower arterial pressure to goal in patients with kidney disease, diabetes, or albuminuria. An integration of the guidelines of the JNC 7, National Kidney Foundation, and American Diabetes Association. #, All patients with diabetes or renal insufficiency, or both, should be instructed on *lifestyle modifications* as per the JNC 7. All patients, however, should be started on therapy if blood pressure is >130/80 mm Hg. Note: If BP < 20/10 mm Hg above goal (130/80 mm Hg), then ACE inhibitor or ARB, titrated to maximal doses, alone may be used. *, Nondihydropyridine CCBs (verapamil and diltiazem have been shown to reduce both CV mortality, proteinuria, and diabetic nephropathy progression independent of ACE inhibitors or ARBs). β-Blockers may be substituted for calcium channel blockers if the patient has angina, heart failure, arrhythmia, or a high heart rate (i.e., >84 beats/min at rest) necessitating their use. β-Blockers with proven efficacy to reduce CV events and the lowest side-effect profile are preferred; of those available, carvedilol meets these criteria. *Note that use of a β-blocker with a nondihydropyridine CCB should be avoided in the elderly and those with conduction abnormalities.* Otherwise, such combinations are safe and particularly effective for lowering blood pressure. NOTE: Other agents, such as minoxidil, hydralazine, and clonidine or methyldopa can be used as adjunctive agents to help achieve goal blood pressure. Clonidine should NOT be used with β-blockers or high-dose verapamil for numerous reasons, not the least of which is a high likelihood of severe bradycardia.

ANTIHYPERTENSIVE AGENTS

Renin Angiotensin-Aldosterone System Blockade

Angiotension-Converting Enzyme Inhibitors

Although early clinical trial data supported the use of ACE inhibitors as agents that may provide additional protection against nephropathy progression, independent of blood pressure, this has not been borne out in larger studies of people with early-stage nephropathy (i.e., stage 2 [GFR 60 to 89 mL/min]).[47,48] In both the posthoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial and in well-controlled animal studies, using 24-hour BP monitors, there was no evidence favoring the concept that ACE inhibitors have unique effects, independent of BP control, on preservation of renal function.[48,49] In addition to ALLHAT, the United Kingdom Prospective Diabetes Study (UKPDS) magnifies the issue that ACE inhibitors are not superior to other antihypertensive agents for reducing cardiovascular risk.[50] In this trial, captopril and atenolol had similar outcomes in hypertensive type 2 diabetic patients. This difference in outcome between trials may relate to several issues. First, in the earlier clinical studies with ACE inhibitors, all patients had advanced kidney disease (i.e., GFR <50 mL/min) and all had more than 500 mg/d proteinuria. Because macroalbuminuria is clearly associated with increased risk of nephropathy progression, a reduction in albuminuria should correlate with preservation of renal function. This has been shown in three postanalyses of large renal outcome trials.[16,17,51] Because ALLHAT had no proteinuria data, it is unclear what its results mean because the benefit of these agents on hard outcomes has been described only in patients with proteinuria and advanced nephropathy. Moreover, meta-analyses support the use of ACE inhibitors as antihypertensive agents in patients with diabetic nephropathy, in part because they reduce proteinuria.[29]

This benefit in people with advanced nephropathy and proteinuria is exemplified by results in the captopril nephropathy trial of people with type 1 diabetes. In this study, those whose serum creatinine values were >2.0 mg/dL derived the greatest benefit from adding ACE inhibition to a standard antihypertensive regimen in order to lower BP to <140/90 mm Hg. The ACE inhibitor group had a 74% reduction in the risk of doubling serum creatinine and a 75% reduction in the incidence of death, dialysis, and kidney transplantation compared with the placebo group. Conversely, patients with a serum creatinine value <1.0 mg/dL and similar degrees of BP reduction with an ACE inhibitor experienced only a 4% reduction in this endpoint. In the REIN trial, patients who had serum creatinine values higher than 2.0 mg/dL and >3.0 g/d proteinuria had a 62% reduction in renal disease progression during the same 42-month follow-up, and those with MA had a 22% reduction in renal disease progression.[52] Similar findings have been noted in meta-analyses of nondiabetic renal disease.

ACE inhibitors have been shown to reduce cardiovascular events in normotensive patients who are at high cardiovascular risk (i.e., patients with type 2 diabetes or ischemic heart disease, or both).[53] Their effects are even more pronounced on cardiovascular (CV) event reduction in the presence of proteinuria or kidney disease.[33,54] ACE inhibitors reduce proteinuria, a known risk factor for CV and renal disease, more than other antihypertensive agents at similar levels of BP lowering.[47] Additionally, unlike ALLHAT, these studies used diuretics as the second agent necessary for BP control, which also may have contributed to the differences in outcome among these studies.

ACE inhibitors may also protect renal function via their effect on "renal reserve." These agents blunt the rise in GFR that follows a protein load.[55] The nephron responds to a variety of factors, such as increased protein intake with an elevation in GFR. This is referred to as *renal reserve* because it reflects the ability of the kidney to increase its clearance rate in the presence of higher urea genesis. The increase in GFR is due to afferent glomerular arteriolar dilation in response to various amino acids.

A simple way to conceptualize the benefits of ACE inhibitors to the kidney is through an analogy with cardiac function. ACE inhibitors reduce the maximal response of a given nephron to excrete metabolic waste products by reducing its baseline GFR, analogous to β-blocker–induced reduction in baseline heart rate, blunting the maximal increase in heart rate and BP during exercise, in part by decreasing the work of the heart and improving coronary flow. β-Blockers reduce cardiac mortality in those with diabetes and kidney disease.[56] When β-blockers are stopped, heart rate and myocardial work increase. We postulate that ACE inhibitors reduce the work of individual functional nephrons in much the same way and thus preserve nephron function.

In keeping with the aforementioned concept, increases in serum creatinine are commonly seen within a few weeks of starting ACE inhibitors and angiotensin receptor blockers (ARBs), especially in those with later-stage nephropathy, who have lost their renal reserve. A rise in serum creatinine limited to 30% to 35% within the first 4 months of starting renin angiotensin-aldosterone system (RAAS) blocking therapy, however, correlates with preservation of kidney function over a mean follow-up period of 3 or more years.[8,57] This correlation between a limited early rise in serum creatinine and long-term preservation of kidney function was restricted to patients with baseline serum creatinine values ≤3.5 mg/dL who were younger than age 66. If acute increases in serum creatinine of >40% occur in less than 4 months of RAAS blocker therapy, the physician should evaluate the patient for (1) volume depletion (the most common etiology); (2) worsened heart failure; or (3) bilateral renal artery stenosis.[57] Elevations in serum potassium become clinically relevant only at levels markedly exceeding 5.5 mEq/L or 5 mEq/L in the presence of digitalis preparations. Hyperkalemia can be addressed by appropriately dosing diuretics and stopping agents known to increase potassium, such as nonsteroidal anti-inflammatory agents and increased intake of fruits and many vegetables.

In summary, the data on ACE inhibitors indicate that they are efficacious in slowing progression of advanced proteinuric nephropathy when used as part of a regimen to achieve BP and proteinuria lowering. In contrast, the data do not support the notion that these agents are superior to other BP-lowering agents for reducing CV mortality or preventing long-term consequences of early stage 2 nephropathy (i.e., GFR > 75 but < 90 mL/min).[58]

Angiotensin Receptor Blockers

Animal data support the concept that ARBs provide renoprotection similar to that of ACE inhibitors.[49] Two renal outcome trials, the Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan in Diabetic Nephropathy Trial (IDNT), demonstrated that in advanced nephropathy secondary to diabetes, use of an ARB as part of an antihypertensive regimen to achieve BP reductions slows nephropathy progression to a greater extent than other agents (i.e., amlodipine or β-blockers/diuretics).[59,60] The primary composite endpoint for both studies was time to doubling of baseline serum creatinine concentration, onset of ESRD, or death. In the RENAAL study of 1513 patients, followed for an average of 3.4 years, and the IDNT of 1715 patients, followed for an average of 2.7 years, there were 16% and 37% risk reductions by losartan and irbesartan, respectively, for the primary endpoint. In RENAAL, there was a 28% reduction in time to ESRD. It was estimated that losartan could delay the need for dialysis or transplantation for 2 years.[59]

These trials clearly reinforce the earlier point about selecting agents that not only help achieve the BP goal but also reduce proteinuria (see Table 35–1). On the basis of these results, all guidelines include ARBs as first-line therapy for patients with diabetes and evidence of nephropathy.[2,8,45]

ARBs appear to be comparable to ACE inhibitors in patients following a myocardial infarction,[27] but only limited data directly compare the two classes in terms of renal outcomes. The COOPERATE trial sought to answer this question by randomizing patients to receive a dose of an ACE inhibitor alone or ARB alone, predefined to yield the greatest reduction in albuminuria. These doses were compared with either ARB or ACE inhibitor alone or in combination on renal outcomes.[61] Although the study found that all three treatment groups had similar reductions in blood pressure throughout the 3 years of the study, patients in the combination group had the greatest reduction in proteinuria and slowest progression to ESRD.[61]

In addition to similar renoprotective properties, ARBs and ACE inhibitors share several other properties: (a) they reduce new-onset diabetes,[62] and (b) they reduce the incidence of recurrent stroke.[63,64] ARBs, however, are generally better tolerated than ACE inhibitors in that they are associated with a lower incidence of cough, angioedema, and hyperkalemia.[65]

Diuretics

Diuretics are the oldest class of antihypertensive agents that have consistently demonstrated their ability to reduce CV mortality. Thiazide diuretics, in particular, have gained a renewed importance in treating hypertension since the publication of ALLHAT.[66] The trial compared the effects of a thiazide diuretic, a dihydropyridine calcium channel blocker, an α–adrenergic blocker, and an ACE inhibitor on CV outcomes in a group of more than 42,000 people at high CV risk with hypertension. The study found no differences in the primary outcome (i.e., fatal CHD or nonfatal myocardial infarction combined) between the treatment groups over the 6-year follow-up. On the basis of these and many other outcome trials, JNC 7 states that diuretics should be used as initial therapy in most (those older than age 50) patient populations.

The beneficial effect of thiazide diuretics in those with diabetes was further demonstrated by programs like Systolic Hypertension in the Elderly, which showed that chlorthalidone, the diuretic used in most positive outcome trials, reduced CV mortality.[67] Although JNC 7 recommends the use of any one of the thiazide-like diuretics, special consideration should be given to the specific thiazide chosen. In the Multiple Risk Factor Intervention Trial, chlorthalidone was shown to be superior to hydrochlorothiazide in terms of CV outcomes. Although the two drugs are thought to have similar efficacy, chlorthalidone is likely more potent because of its longer half-life (44 hours, chlorthalidone vs. 12 hours, hydrochlorothiazide).[68,69] This difference in duration of action translated into an additional 7 mm Hg reduction in systolic BP when substituted for hydrochlorothiazide.[68]

In general, thiazide diuretics are quite effective in patients who have serum creatinine values <1.7 mg/dL. At higher levels of serum creatinine or if the estimated GFR is <50 mL/min, only loop diuretics given twice daily are effective for volume removal and BP reduction. For diuretic-resistant patients, generally those with hypoalbuminemia or heart failure, combining a diuretic that inhibits at the loop of Henle with one that acts at the proximal or distal tubule, such as furosemide with metolazone, may yield a response when neither is effective alone.

Clinicians should avoid excessive diuresis, as well as interference with diuretic action by nonsteroidal anti-inflammatory drugs (NSAIDs). Potassium-sparing diuretics should also be avoided in patients with preexisting hyperkalemia (i.e., serum potassium > 5.5 mEq/L from either diabetes or severe renal disease of other etiologies). Use of aldosterone receptor antagonists, such as spironolactone and epleronone in low doses, may be indicated in heart failure and renal insufficiency or in proteinuric kidney disease, as they have been shown to be protective both in human heart failure and in animal models of renal disease.[70-72] When used with other diuretics at low doses, the incidence of hyperkalemia with aldosterone receptor antagonists was low in the heart failure trials. A benefit of significant risk reduction occurred when added to maximal therapy including an ACE inhibitor, β-blocker, and nitrates in heart failure, and there were additive antiproteinuric effects to ACE inhibitors or ARBs in diabetes.

Although moderate to high doses of diuretics worsen insulin resistance and increase the risk for new-onset diabetes, at the currently recommended low doses or when they are taken in combination with an ACE inhibitor or ARB, their effects on insulin sensitivity and other metabolic parameters are negligible.[73] Sodium restriction is critically important in all patients taking diuretics, as sodium intake in excess of 200 mEq/day not only blunts the antihypertensive and antiproteinuric actions of the ACE inhibitors but also increases the risk of hyperkalemia development.

Calcium Channel Blockers

The available data from both preclinical and clinical studies indicate that dihydropyridine calcium channel blockers, such as amlodipine, do not reduce albuminuria to the same extent as nondihydropyridine calcium channel blockers, such as verapamil or diltiazem.[74,75] The mechanism for this difference in advanced nephropathy relates to differences in glomerular permeability.[75,76] This difference in antiproteinuric effect

has translated into poorer renal outcomes in advanced nephropathy with proteinuria compared with blockers of the RAAS.[75]

This effect on proteinuria, however, is only relevant in advanced nephropathy. In the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), which compared nondihydropyridine calcium channel blockers with ACE inhibitors, alone or in combination, in patients with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion, no significant effect was seen with verapamil alone.[77] MA development, the primary endpoint, occurred with similar frequency in the verapamil and placebo group. This is not surprising because the calcium channel blockers (CCBs) are not considered agents that affect inflammation of the vasculature, which is reflected by the presence of microalbuminuria.[14,38,78]

Earlier concerns about safety of calcium channel blockers in hypertensive patients have been unfounded on the basis of trial results.[66] However, in advanced proteinuric kidney disease, both animal models and human studies show a failure of dihydropyridine CCBs, when used in the absence of an ACE inhibitor or ARB, to optimally slow nephropathy progression despite BP reduction.[60,79] Thus the NKF notes that dihydropyridine CCBs should not be given in the absence of an ACE inhibitor or ARB maximally dosed to reduce BP in patients with proteinuric kidney disease, regardless of etiology.

β-Adrenergic Blockers

Despite a high adverse-effect profile, β-blockers reduce CV mortality in high-risk patients.[56] In the UKPDS study, atenolol was as effective as captopril in both arterial pressure lowering and protection against microvascular and macrovascular disease.[50] In a large meta-analysis of more than one million high CV-risk people, β-blockers offered a high degree of protection against myocardial events, albeit less for stroke protection.[80] Thus, although these agents are not considered first-line agents except under certain compelling circumstances, they are excellent add-on agents to reduce risk and achieve BP targets.

Newer agents in this class have neutral or beneficial effects on metabolic and renal profiles. One α- and β-blocker of note is carvedilol. This agent has demonstrated reduced CV morbidity and mortality rates and also has a neutral effect on glycemic and lipid parameters, as well as a reduced risk of new-onset MA in patients with hypertension and diabetes.[81] Moreover, it has been shown to reduce mortality in people with nephropathy.[82] This may be a useful β-blocker for such high-risk patients.

α-Adrenergic Blockers

α-Adrenergic antagonists, although effective in reducing BP, have not been shown to slow renal disease progression or reduce albuminuria in either animal models or patients with type 2 diabetes.[83] This class of agents also fails to reduce CV events in patients who have or develop heart failure. This is evidenced by the results of the long-acting α-blocker arm of ALLHAT, which was stopped early due to increased events.[84] Hence, this class is not a preferred modality of initial treatment for hypertension in those with kidney disease, despite its favorable metabolic profile. α-Adrenergic blockers are useful as third-line treatment for hypertension, especially in older men with urinary stream problems.

TREATMENT RECOMMENDATIONS AND CAVEATS

The goal BP for patients with renal disease or diabetes, or both, as outlined by all guidelines is <130/80 mm Hg. The average number of agents necessary to approach this goal in clinical trials has been 3.3 agents at maximally tolerated doses (Fig. 35–4). A retrospective analysis of renal outcome trials (i.e., people with baseline GFR values <50 mL/min) demonstrates that those with BPs that approach 130/80 mm Hg have slower rates of decline in kidney function (Fig. 35–5). Lowering BP to this range also slows progression of advanced kidney disease to a greater extent than allowing pressures to remain elevated. Guidelines for control of hypertension in patients with diabetes from various international consensus committees are summarized in Table 35–3.

The NKF and American Diabetes Association (ADA) guidelines make the point that antihypertensive agents with the ability to reduce both BP and albuminuria are preferred first-line agents to preserve kidney function[8,85] (see Fig. 35–3).[8,45] Thus, the optimal initial therapy for hypertensive diabetic patients is a blocker of the RAAS because of proven efficacy in both of these areas and excellent tolerability. If

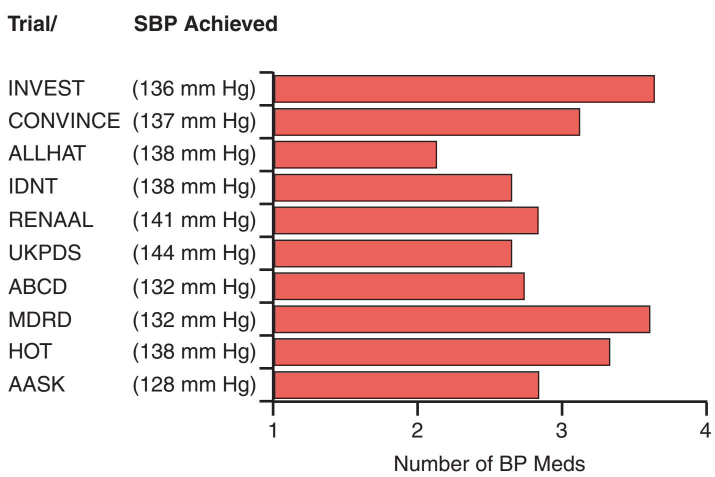

Figure 35–4 Number of antihypertensive medications required to achieve blood pressure goals in major clinical trials over the past decade.

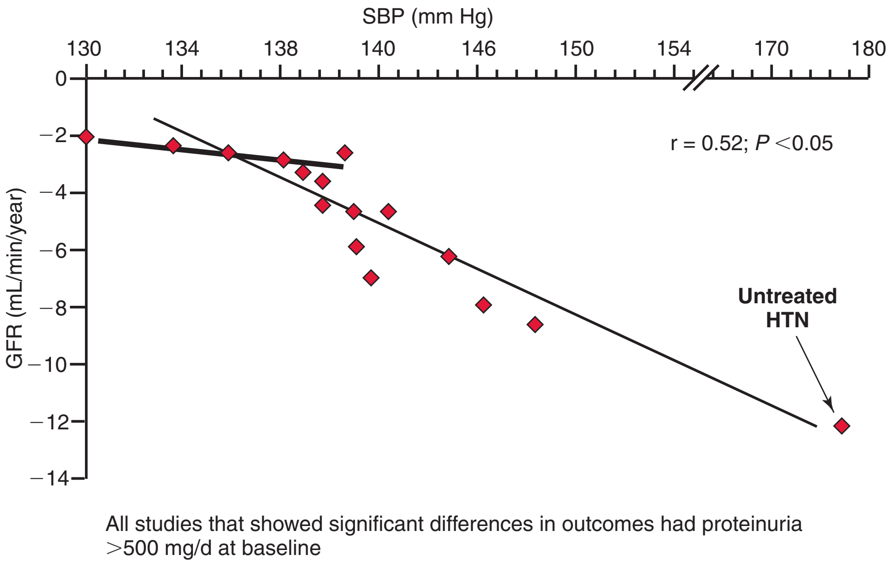

Figure 35–5 The relationship between achieved level of blood pressure and rate of decline in renal function in renal outcome trials over the past decade.

Table 35–3 Summary of Guidelines for Control of Hypertension in People with Kidney Disease or Diabetes from Various Consensus Committees Around the World

Group	Goal Blood Pressure (mm Hg)	Initial Therapy
American Diabetes Association (2005)	<130/80	ACE Inhibitor/ARB*
Japanese Hypertension Society (2005)	≤130/80	ARB*†
National Kidney Foundation (2004)	<130/80	ACE Inhibitor/ARB*
British Hypertension Society (2004)	≤130/80	ACE Inhibitor/ARB
JNC 7 (2003)	<130/80	ACE Inhibitor/ARB*
ISH/ESC (2003)	<130/80	ACE Inhibitor/ARB
Canadian Hypertension Society (2002)	≤130/80	ACE Inhibitor/ARB
Australia-New Zealand (2002)	<130/85	ACE Inhibitor
WHO/ISH (1999)	<130/85	ACE Inhibitor

*Indicates use of combination therapy with a diuretic if blood pressure is substantially higher than goal.
†Calcium antagonists could also be combined.

the BP at baseline is >20/10 mm Hg above the goal (i.e., >150/90 mm Hg when the goal is <130/80 mm Hg), the combination of a RAAS blocker with a thiazide diuretic is appropriate. In cases of allergies to thiazides, then CCBs may be substituted. A vasodilating β-blocker should be strongly considered as an early add-on for BP control and should be preferred to a CCB if pulse rate is >84 beats/min.[46] A central α-adrenergic agonist, such as clonidine, is appropriate if β-blockers are contraindicated.

The potential risks of aggressive BP lowering, particularly in elderly patients with type 2 diabetes, has caused concern. Reducing diastolic BP to <80 mm Hg has been thought to increase CV risk in this group, but no convincing evidence of this possibility has been found in prospective clinical trials.[50,86] Retrospective data analyses of data suggested that there might be a J-shaped relationship between diastolic BP and CV disease mortality in patients with established symptomatic coronary artery disease or unstable angina. However, a posthoc analysis of three separate renal outcome trials has failed to demonstrate a J curve for BP until levels get to <115/55 mm Hg.[79,87] Thus the putative J curve should not serve as a deterrent to lowering BP to recommended goals in the absence of any clear evidence of coronary disease or unstable angina.

BP goal should be achieved within 3 to 4 months in most patients, longer in those with previous strokes or autonomic dysfunction. BP should be monitored with patients in both the sitting and the upright position to exclude the possibility of orthostatic hypotension because autonomic denervation is frequent among patients with type 2 diabetes who have nephropathy and polyneuropathy.

Data from NHANES 1999-2000 in the cohort with diabetes reported that only about 32% achieved the BP goal of <130/80 mm Hg, while the goal for Healthy People 2000 was 50%.[88] Many reasons exist, both on the part of the patient and the physician, for not achieving this lower BP goal in a higher percentage of the patients. One main reason for the failure to achieve this goal is inadequate drug dosing, which is related to emotion-based rather than evidence-based medicine. Physicians recall that there are increased side effects of drugs as doses increase. Although this is true for older antihypertensive agents, it is not true for ACE inhibitors or ARBs. Thus to optimize CV and renal risk reduction, physicians should establish BP, lipid, and glucose goals in writing with their patients, keep a copy in the chart, and give one to the patient. In order to maximize reduction in CV and renal mortality, the patient and the physician should be aware of treatment goals and discuss progress toward them at each visit.

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Resistant Hypertension

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CHAPTER CONTENTS

DEFINITION

Resistant hypertension is defined as blood pressure (BP) that remains uncontrolled despite the use of three antihypertensive agents. Ideally, one of the agents should be a diuretic and all of the agents should be prescribed at doses that provide maximal or near-maximal benefit. Patients with resistant hypertension are at high risk of having reversible causes of hypertension and therefore may benefit from special diagnostic and therapeutic considerations. Historically, the definition of resistant hypertension has required obligatory use of a diuretic. Although a diuretic is, in general, useful in maximizing antihypertensive treatment, a group of patients cannot or will not use a diuretic because of real or perceived adverse effects. Such patients, if failing multidrug regimens, will likely benefit from being identified as having resistant hypertension because they are also at increased risk of having reversible causes of hypertension.

The traditional definition of resistant hypertension described uncontrolled hypertension with use of three or more medications, the implication being that, if the blood pressure is controlled, regardless of the number of medications required, then resistant hypertension is excluded. Such an interpretation does not reflect the degree of drug resistance among patients with controlled hypertension. Patients requiring four, five, or six antihypertensive medications are clearly resistant to treatment and have an increased likelihood of having potentially reversible causes of hypertension. With the current definition, patients requiring more than three antihypertensive agents, even if their BP is controlled, are considered to have resistant hypertension and deserve aggressive diagnostic evaluation.

PREVALENCE

The prevalence of resistant hypertension is unknown because accurately determining the percentage of patients whose BP cannot be controlled with three agents would require a forced-titration study of a large hypertensive cohort. However, resistance to antihypertensive therapy is clearly common, as indicated by cross-sectional analyses and clinical trials. In the most recent National Health and Nutrition Examination Survey (NHANES 1999-2000), only 53% of persons being treated for hypertension were controlled to <140/90 mm Hg.[1] The control rate in treated persons 60 years of age or older was only 44%. In a cross-sectional evaluation of primary care patients in Germany, the control rate in obese persons (BMI ≥30 kg/m^2) receiving treatment for high BP was <20% in both men and women.[2] A similar evaluation of diabetic patients in the United States found that only 23% of African-American and 31% of Caucasian patients were controlled to <130/80 mm Hg despite being prescribed an average of 2.7 and 2.2 antihypertensive medications, respectively.[3]

Contemporary hypertension outcome trials may provide the best estimate of the prevalence of resistant hypertension. In these studies the medications are usually provided at no charge to subjects, adherence is monitored, and the protocols mandate continued titration if the BP remains above goal. These studies likely underestimate the true prevalence of resistant hypertension because patients with known drug resistance are generally excluded from enrolling. Even with this limitation, these trials demonstrate that resistant hypertension is common.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) may be the most relevant in estimating the prevalence of resistant hypertension in the United States because it is the largest outcome trial to date, enrolling more than 42,000 subjects, and is ethnically diverse, with 35% of subjects being African American or Afro-Caribbean.[4] In ALLHAT, subjects 55 years of age or older were randomized to chlorthalidone 12.5 to 25 mg, amlodipine 2.5 to 10 mg, lisinopril 10 to 40 mg, or doxazosin 2 to 8 mg daily with additional agents from other classes added as needed if BP remained >140/90 mm Hg. After 5 years of follow-up, 34% of subjects remained uncontrolled with an average use of

2 antihypertensive medications and approximately 27% of subjects were receiving 3 or more medications.

In ALLHAT, approximately 8% of subjects were prescribed four or more medications.[5] This percentage, added to the percentage of subjects who remained uncontrolled on three medications, should approximate the prevalence of resistant subjects in ALLHAT (it would not include the subjects uncontrolled on fewer than three medications who would have ended up needing four or more medications). This combined figure is not yet available from the published ALLHAT data. If one third of the subjects on three medications were never controlled (the same rate achieved overall), this percentage added to subjects on four or more medications would be about 15% of the entire cohort. A 15% prevalence of resistant hypertension is likely an underestimate relative to similarly aged hypertensive patients because subjects with known resistant hypertension (i.e., uncontrolled on more than two antihypertensive medications) were excluded from ALLHAT.

Although the percentage of patients with resistant hypertension (based on needing four or more medications) cannot be determined from published data, other clinical trials are consistent with ALLHAT in demonstrating a high degree of uncontrolled hypertension despite use of multidrug regimens. In the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, hypertensive persons at least 55 years of age and with 1 cardiovascular risk factor other than hypertension were randomized to controlled-onset, extended-release verapamil or atenolol or hydrochlorothiazide.[6] Other agents were added in stepwise fashion as needed for uncontrolled hypertension. At the end of the study, 33% of the subjects remained uncontrolled (<140/90 mm Hg) with 18% of subjects being on three or more medications. In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) study, hypertensive persons at least 50 years of age with multiple cardiovascular risk factors were randomized to valsartan or amlodipine with hydrochlorothiazide and other agents being added to lower BP to <140/90 mm Hg.[7] At 30 months of follow-up, 40% of subjects had not achieved goal BP. Among the 15% of subjects receiving 3 or more drugs, BP remained elevated in 61%.

These cross-sectional and outcome studies suggest that resistance to multidrug antihypertensive regimens is not uncommon. Extrapolation from the ALLHAT results suggests that at least 15% of older hypertensive persons may have resistant hypertension. Further analysis of the ALLHAT database will allow for a more definitive estimate of the prevalence of resistant hypertension in the United States.

PROGNOSIS

The long-term outcome of patients with resistant hypertension compared with patients with more easily controlled hypertension has not been assessed. Presumably, cardiovascular risk is increased, given that patients with resistant hypertension often have had a longstanding history of severe hypertension and risk has been shown to be directly related to BP. Further, patients with resistant hypertension have a high prevalence of concomitant conditions (diabetes, sleep apnea, endothelial dysfunction, left ventricular hypertrophy, chronic kidney disease) that contribute to cardiovascular disease outcomes.

PATIENT CHARACTERISTICS

Treatment-resistant hypertension is generally due to persistently high systolic BP. In ALLHAT, systolic BP remained elevated at 3 years in 36% of subjects, while diastolic BP remained elevated in only 10%.[5] Similarly, in the VALUE trial, systolic BP at 30 months follow-up remained elevated in 38% of subjects, while diastolic BP was uncontrolled in only 10%.[7] In CONVINCE after 2 years of treatment, systolic BP was >140 mm Hg in 30% of subjects compared with 10% of subjects in whom diastolic BP was >90 mm Hg.[6]

Older age is one of the strongest predictors of poor blood pressure control. In NHANES III, the highest relative risk of uncontrolled hypertension, which includes untreated and undertreated hypertension, as well as resistant hypertension, was in those 65 years of age or older.[1] Among treated persons, BP was controlled in 65% of those 25 to 44 years old, 52% of those 45 to 64 years old, and 34% of those 65 years old or older. In the Framingham Heart Study, cross-sectional analysis indicated that increasing age was significantly associated with uncontrolled systolic BP.[8] In a prospective observation, those 55 years of age or older were only two thirds as likely to have controlled BP as subjects younger than 55 years of age.[9] In ALLHAT, older age also predicted lack of BP control. In participants 55 to 59 years old, the control rate for systolic BP was 62%, while in those 80 years old or older, control rates were less than 50%.[5]

In general, the more severe the hypertension, the more medications are necessary to effectively achieve goal BP. In the Framingham Heart Study, participants with systolic BP levels >160 mm Hg were twice as likely to remain uncontrolled as those with systolic BPs between 140 and 159 mm Hg.[9] Likewise, in ALLHAT, higher baseline systolic BP levels were strongly associated with a lower likelihood of reaching goal BP.[5]

Other patient characteristics associated with resistant hypertension include obesity, diabetes, chronic kidney disease, black race, female sex, and the presence of left ventricular hypertrophy (LVH). In both cross-sectional studies and treatment trials, obesity is associated with use of an increased number of antihypertensive medications and an increased likelihood of never achieving BP control. Clinical trials indicate that diabetics are more resistant to antihypertensive treatment than nondiabetics, requiring more medications to achieve the same level of BP reduction. In general, as renal function declines, more antihypertensive medications are required and achievement of goal BP becomes progressively less likely. Black race and female sex are also associated with increased resistance to treatment. In ALLHAT, BP control rates were best in nonblack men (70%) and worst in black women (59%).[5] Presence of LVH also predicts difficulty in achieving BP control, but it is unknown if LVH merely reflects more severe hypertension or has an independent effect on treatment resistance. Further, regional differences in BP control have been observed. In ALLHAT control rates were worse in participants living in the Southeastern United States.[5] The reason for this regional effect is unknown, but it was not due to use of fewer medications.

GENETICS

Because resistant hypertension represents an extreme phenotype of a much more common disorder, it seems likely that

genetic causes may be more prevalent than in the general hypertensive population, but few genetic screenings of this high-risk subgroup have been conducted. In one evaluation, Finnish persons with treatment-resistant hypertension were screened for mutations in the epithelial sodium channel (ENaC).[10] Such mutations can cause constitutive activation of ENaC, resulting in Liddle's syndrome, characterized by inappropriate sodium and fluid retention, which would be expected to suppress both renin and aldosterone. Genetic variants of ENaC subunits were significantly more common in the Finnish subjects with resistant hypertension compared with normotensive controls, but presence of the variants was not related to renin or aldosterone levels. Thus it was not obvious that the higher prevalence of the genetic variants had a meaningful physiologic effect.

Allele variants of CYP3A5, an enzyme that catalyzes the metabolization of cortisol and corticosterone, have been linked to higher BP levels in African Americans. In a subgroup analysis of a larger evaluation, presence of the CYP3A5*1 allele was associated with treatment-resistant hypertension in black subjects.[11] Although the study is small, it is provocative in suggesting a possible genetic cause of resistant hypertension and supports broader genetic screenings of similar patients.

ADHERENCE

Nonadherence is an important cause of uncontrolled hypertension, which is distinct from resistant hypertension. The diagnosis of resistant hypertension requires demonstration of failure of a three-drug regimen that is taken correctly. In general hypertensive populations, nonadherence to prescribed antihypertensive therapies may exceed 60% over several years of follow-up.[12] Multidrug regimens, complicated dosing regimens, and frequent medication changes worsen adherence.[13]

Although nonadherence is a common cause of lack of BP response in the general hypertensive population, it is likely to be less common in those who are referred to and keep their appointments with specialists. In an analysis of patients referred to and seen by hypertension specialists at Rush University Medical Center, investigators estimated that lack of BP control was attributable to medication nonadherence only 16% of the time.[14] This suggests that most nonadherent patients are effectively recognized by primary care physicians before referral or that nonadherent patients decline referral to specialists for their poorly controlled hypertension, or both.

Ultimately, nonadherence can only be confirmed by patient self-report. Therefore establishing and maintaining good rapport with the patient is essential. Adherence should be discussed in a nonthreatening fashion with particular attention being paid to out-of-pocket costs, dosing regimens, and possible adverse effects. The input of family members, in the presence of the patient, should be encouraged. Nonadherence might be suspected in patients chronically unfamiliar with the prescribed medications or dosing schedules or in whom anticipated adverse effects are absent, or both.

WHITE COAT EFFECT

Significant white coat effects (elevated office but normal or significantly reduced ambulatory BP levels) are likely as common in patients with resistant hypertension as in those with more easily controlled hypertension, with a prevalence of 20% to 30%.[15,16] As in general hypertensive populations, patients with resistant clinic hypertension but lower ambulatory BP levels are probably at lower risk of cardiac complications than those with higher ambulatory BP levels.[17] Unknown is to what degree antihypertensive medications can be withdrawn from patients with "white coat" resistant hypertension and low ambulatory BP levels.

White coat effects should be suspected in patients with persistently high BP levels measured in the clinic but much lower levels when measured outside of the clinic (home or work); in patients with high BP levels measured in the clinic but symptoms of low BP, particularly orthostatic symptoms; and in patients with sustained clinic hypertension but an absence of evidence of target-organ damage (LVH, retinopathy, chronic kidney disease). In such cases, 24-hour ambulatory monitoring is indicated to evaluate for a significant white coat effect. If present, out-of-clinic BP measurements should be relied on to guide therapy.

DIETARY SODIUM

On a population basis, high dietary salt ingestion is related to increased BP levels.[18] In hypertensive persons, high salt ingestion has been shown to blunt the antihypertensive benefit of pharmacologic therapy.[19] Studies of dietary salt restriction demonstrate reductions in systolic BP in salt-sensitive hypertensive persons of up to 5 to 10 mm Hg.[20,21] BP reductions in salt-sensitive subgroups, such as African Americans, the elderly, the obese, and patients with chronic kidney disease, tend to be larger than in the general hypertensive population, where treatment effects of dietary sodium reduction are generally in the range of 2 to 8 mm Hg in systolic BP. Benefit of dietary salt restriction has not been specifically evaluated in patients with resistant hypertension, but benefit has been described in hypertensive subjects uncontrolled with an ACE inhibitor or an ACE inhibitor in combination with a diuretic.[22,23] Accordingly, dietary salt restriction, ideally to <100 mEq of sodium/24-hour, should be recommended to all patients with resistant hypertension.

OBESITY

Obesity is associated with more severe hypertension, need for an increased number of antihypertensive medications, and increased likelihood of never achieving BP control.[2,5] Mechanisms of obesity-induced hypertension are complex and not fully elucidated but include impaired sodium excretion, increased sympathetic activation, and stimulation of the renin-angiotensin-aldosterone system.[24] Benefit of weight reduction has not been specifically evaluated in persons with resistant hypertension. In a review of long-term weight-reduction studies, a 10-kg weight loss was associated with a 6 mm Hg reduction in systolic and a 5 mm Hg reduction in diastolic BP.[25] Although admittedly difficult to accomplish and even more difficult to maintain, weight reduction should be recommended to all overweight and obese patients with resistant hypertension because it will likely assist BP reduction and reduce the need for antihypertensive treatment.

ALCOHOL

Heavy alcohol ingestion is associated with a significantly increased risk of having hypertension that is uncontrolled with treatment. In a cross-sectional analysis of Chinese adults, ingesting ≥30 drinks a week increased the risk of having hypertension by 12% to 14%.[26] In a Finnish hypertension clinic, patients with elevated γ-glutamyltransferase (GGT) levels, a marker of heavy alcohol ingestion, were much less likely to have their BP controlled during a 2-year follow-up compared with patients with normal GGT levels.[27] Prospectively, cessation of heavy alcohol ingestion by a small group of patients reduced 24-hour ambulatory systolic BP by 7.2 mm Hg and diastolic BP by 6.6 mm Hg while reducing the prevalence of hypertension from 42% to 12%.[28] Whether through direct physiologic effects or improvements in adherence, or both, cessation of heavy alcohol use does improve hypertension control. Ingestion should be limited to 1 oz of alcohol a day (24 oz of beer, 10 oz of wine, or 2 oz of 100-proof liquor).

EXOGENOUS SUBSTANCES

Pharmacologic substances that can worsen BP control include non-narcotic analgesics, glucocorticoids, stimulants, sympathomimetics, and oral contraceptives (Table 36–1). The effects on BP of these substances vary widely among individuals, with most persons being able to tolerate them with no or minimal increases in BP. Some individuals, however, may be particularly sensitive to specific agents such that withdrawal should be attempted if possible.

Chronic use of non-narcotic analgesics including aspirin, acetaminophen, and nonsteroidal anti-inflammatory agents (NSAIDs) increases the risk of developing hypertension.[29,30] The effect is presumably from increased sodium and fluid retention caused by inhibition of prostaglandins in the kidney. Meta-analyses of the effects of NSAIDs have indicated average increases in mean arterial pressure of approximately 5.0 mm Hg.[31] NSAIDs can antagonize the effects of antihypertensive treatment, particularly ACE inhibitors, ARBs, and β-blockers.[32,33] These effects can also occur with selective cyclooxygenase-2 (COX-2) inhibitors, though perhaps to a lesser extent.[34,35]

Table 36–1 Exogenous Substances That Can Contribute to Development of Resistant Hypertension

Dietary salt
Non-narcotic analgesics
Nonsteroidal anti-inflammatory agents including selective COX-2 inhibitors
Acetaminophen
Alcohol
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine)
Sympathomimetic agents (decongestants, diet pills, cocaine, caffeine)
Oral contraceptives
Cyclosporine
Erythropoietin
Licorice

Although the average effect on BP of non-narcotic analgesics is modest, effects may be much more pronounced in some individuals. In sensitive individuals, significant increases in BP, fluid retention, or acute renal insufficiency may occur. Elderly patients, diabetics, and patients with chronic kidney disease are at increased risk of manifesting these adverse effects. Accordingly, in patients with resistant hypertension, non-narcotic analgesics should be reduced or even withdrawn if clinically possible.

Amphetamine-like stimulants, such as methylphenidate or dextroamphetamine, may increase BP or worsen BP control, or both. Glucocorticoids increase BP by causing sodium and fluid retention. Sympathomimetics, such as certain decongestants or diet pills, can raise BP. Oral contraceptives generally have modest effects on BP, but large increases can occur in some individuals. Cyclosporine and erythropoietin cause predictable increases in BP. Control can worsen with any of these agents, so BP should be monitored closely during their use. In patients with poorly controlled hypertension, these agents should be discontinued or reduced in dosage if possible.

SECONDARY HYPERTENSION

The most common secondary causes of resistant hypertension are obstructive sleep apnea, hyperaldosteronism, renal parenchymal disease, and renal artery stenosis (Table 36–2). The prevalence of secondary causes of hypertension increases with age largely due to an increasing prevalence of sleep apnea, chronic kidney disease, and renal artery stenosis.[36] Obstructive sleep apnea is particularly common in patients with resistant hypertension, with a prevalence exceeding 80%.[37] Prospective evaluations indicate that hyperaldosteronism is also a common cause of drug resistance, being present in approximately 20% of patients with difficult-to-control hypertension.[38]

OBSTRUCTIVE SLEEP APNEA

Untreated sleep apnea is strongly associated with an increased risk of having high BP, and sleep apnea increases the risk of becoming hypertensive.[39,40] Sleep apnea is more severe in patients with uncontrolled hypertension versus those with good BP control.[41] Also, persons with sleep apnea are less likely to achieve BP control with pharmacologic therapy than persons with similar body mass index but without sleep apnea.[42]

Obstructive sleep apnea is particularly common in patients with resistant hypertension. In a prospective study of 41 patients referred for evaluation of poorly controlled hypertension,

Table 36–2 Secondary Causes of Resistant Hypertension

Obstructive sleep apnea
Hyperaldosteronism
Renal parenchymal disease
Renal artery stenosis
Cushing's disease
Pheochromocytoma

83% were found to have unsuspected sleep apnea, with an apnea/hypopnea index of ≥10 events per hour determined during overnight sleep evaluation.[37] Nearly all of the men had sleep apnea, with a prevalence of 96% versus 65% of the women. This contrasts with a prevalence of sleep apnea of 24% in unselected middle-aged men and 9% in middle-aged women, based on an apnea/hypopnea index of ≥5.[43]

The mechanisms by which sleep apnea may contribute to antihypertensive treatment resistance are not fully elucidated. The best documented pathophysiologic mechanism to date is that sleep apnea induces intermittent hypoxemia, which, in turn, stimulates sustained increases in sympathetic output, which increases BP by increasing vascular resistance and cardiac output.[44,45] Preliminary studies in our laboratory have linked a risk of sleep apnea to hyperaldosteronism.[46] If confirmed, this would suggest that sleep apnea may independently stimulate aldosterone release.

The BP effects of treating sleep apnea with continuous positive airway pressure (CPAP) in patients with resistant hypertension have not been extensively evaluated. In a small, uncontrolled study, 2 months of CPAP use in 11 patients with uncontrolled hypertension reduced 24-hour systolic BP by 11 mm Hg and diastolic BP by 5 mm Hg. In this study, CPAP adherence averaged only 4 hours a night.[47] Although these results are provocative, randomized studies of CPAP in patients with uncontrolled hypertension are necessary to elucidate the antihypertensive benefit.

HYPERALDOSTERONISM

Prospective studies indicate that the prevalence of primary aldosteronism increases with worsening severity of the underlying hypertension. In one of the largest studies, more than 600 persons were evaluated for hyperaldosteronism.[48] Severity of hypertension was determined after withdrawal from antihypertensive treatment. The prevalence of primary aldosteronism was 6% overall and was positively related to the underlying severity of hypertension. In patients with stage 1 hypertension (<160/100 mm Hg), the prevalence of primary aldosteronism (2%) was not different from that in normotensive control subjects. In patients with BP between 160 and 179/100 and 109 mm Hg, the prevalence of primary aldosteronism was 8%, and in those with BP >180/110 mm Hg, the prevalence was 13%.

Several studies have been consistent in diagnosing primary aldosteronism in approximately 20% of patients with resistant hypertension (Fig. 36–1). In our own study at the University of Alabama at Birmingham, we evaluated 90 consecutive subjects with uncontrolled hypertension despite use of an average of 4 medications.[38] On the basis of suppressed renin activity and high 24-hour urinary aldosterone excretion in the setting of high dietary sodium ingestion, 20% of these were diagnosed with primary aldosteronism. These results are similar to those reported by investigators in Seattle, Washington and Oslo, Norway who reported a prevalence of primary aldosteronism in patients with resistant hypertension of 17% and 23%, respectively.[49,50]

The reason for the extremely high prevalence of aldosterone excess in patients with resistant hypertension remains unknown. Reports relating aldosterone excretion to obesity and sleep apnea potentially link three common characteristics of patients with resistant hypertension, but the mechanisms involved have not been identified.[46]

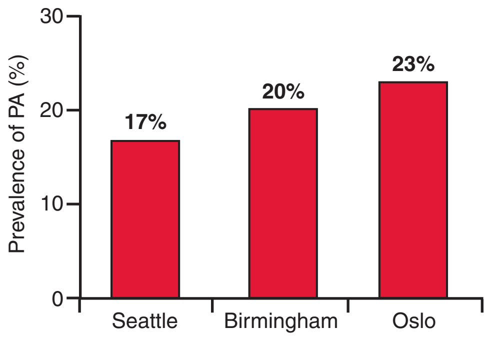

Figure 36–1 Prevalence of primary aldosteronism *(PA)* in patients with resistant hypertension as reported by three different laboratories.[38,49,50]

All subjects with resistant hypertension should be screened for primary aldosteronism, given its high prevalence. Since the large majority of patients diagnosed with primary aldosteronism are not hypokalemic, normal serum potassium levels should not preclude screening.[48] Screening is best accomplished by measuring a morning plasma aldosterone and renin concentration or plasma renin activity. Except for mineralocorticoid receptor antagonists, antihypertensive medications need not be discontinued with the initial screening, as the different classes of agents tend to either increase renin levels or suppress aldosterone levels, such that low renin and high aldosterone levels in the setting of ongoing treatment increase suspicion of aldosterone excess.[51] A suppressed renin level (<10 mUnits/mL) or renin activity (<1.0 mg/mL/min) and a high plasma aldosterone ≥15 ng/dL is suspicious but not diagnostic for primary aldosteronism and should be followed up by a clinician experienced in working up hyperaldosteronism (see Chapter 32). Hyperaldosteronism generally responds well to treatment, either with use of mineralocorticoid antagonists or with surgical resection of an aldosterone-producing adenoma.

RENAL PARENCHYMAL DISEASE

Chronic kidney disease is a common cause or complication, or both, of resistant hypertension. Patients with renal insufficiency often have volume-dependent hypertension secondary to excess sodium and fluid retention. Elevated serum creatinine suggests underlying renal insufficiency, but creatinine levels can be misleading, being normal in many persons with significant loss of kidney function. This is particularly true in the elderly. In all patients with resistant hypertension, renal function should be assessed by estimation of the glomerular filtration rate or by calculation of creatinine clearance.[52] In hypertensive patients with chronic kidney disease, restriction of dietary salt intake is particularly important. In addition, such patients will almost always require the use of diuretics, frequently loop diuretics, to control BP and manage fluid and electrolyte balance. ACE inhibitors or ARBs should be prescribed preferentially in an attempt to slow continued renal functional decline (see Chapter 35).

RENAL ARTERY STENOSIS

Renal artery stenosis is common in patients with hypertension with a prevalence of 20% at the time of coronary angiography.[53] Unknown, however, is the percentage of these lesions that are clinically relevant in terms of producing renovascular hypertension. Also unknown is the prevalence of clinically meaningful renal stenotic lesions in patients with resistant hypertension, although it is undoubtedly substantially higher than in patients with more easily controlled hypertension. The prevalence of renal artery stenosis increases with age and in the presence of aortic or peripheral arterial disease, or both.

More than 90% of renal artery lesions are atherosclerotic in origin. Clues to the diagnosis of atherosclerotic renal artery stenosis include older age; known atherosclerotic disease, especially peripheral arterial disease; unexplained renal insufficiency; and a history of flash pulmonary edema. Less than 10% of lesions are fibromuscular in etiology. These develop most commonly in women younger than 50 years of age.

Noninvasive screening for renal artery stenosis can be difficult. Duplex ultrasound and magnetic resonance angiography have good test characteristics in published studies, but the actual predictive value varies according to institutional experience. Equivocal or even negative studies in patients in whom there is a high level of suspicion may warrant repeat imaging with a different modality.

Angioplasty of fibromuscular lesions almost always benefits and often cures the associated hypertension and therefore is the recommended treatment of choice. Restenosis rates, however, may exceed 20% after 1 year.[54] In contrast, there is considerable controversy regarding medical versus endovascular treatment of atherosclerotic lesions. In patients with controlled BP, the relative benefit of intensive medical therapy versus angioplasty with stenting has not been clearly established. Such clarification is also lacking in patients with resistant hypertension, but given the known cardiovascular risks of poorly controlled hypertension, a general recommendation in favor of revascularization seems appropriate (see Chapter 33).

HISTORY AND PHYSICAL EXAMINATION

Evaluation of the patient with resistant hypertension should focus on identifying factors contributing to treatment resistance and documenting of the degree of target-organ damage. In most patients, causes contributing to the development of resistant hypertension are multiple including lifestyle, use of exogenous substances, and secondary causes of hypertension. Potential contributing factors should be screened for history, physical examination, biochemical evaluation, and radiographic imaging, as appropriate.

Special attention should be given to use of good BP measuring technique including having the patient sit quietly for 3 to 5 minutes before taking BP readings and using correctly sized cuffs to avoid falsely high readings. Supine and upright BPs should be measured at baseline and during follow-up to avoid orthostatic complications. Ambulatory BP monitoring is appropriate to screen for significant white coat effects. Acquisition of a 24-hour urine collection during the patient's normal dietary intake is recommended because dietary sodium and potassium ingestion, creatinine clearance, protein excretion, and aldosterone excretion can be quantified.

TREATMENT

Treatment of resistant hypertension is predicated on identifying and reversing contributing and secondary causes, which are almost always multiple. Rarely does a patient present with a single underlying cause of resistant hypertension. On the basis of observational studies, patients with resistant hypertension are typically obese and sedentary, ingest excessive amounts of sodium, and have sleep apnea. These factors should be anticipated and addressed if present.

Patients should be queried regarding barriers limiting adherence. Lifestyle changes including weight loss, dietary salt restriction, and regular exercise should be encouraged and emphasized regularly during follow-up. Withdrawal of exogenous substances that may interfere with pharmacologic treatment should be attempted if clinically possible. Sleep apnea should be evaluated for by polysomnographic monitoring and treated if present.

Pharmacologic therapy requires use of effective multidrug regimens. The combination of an ACE inhibitor or ARB, a calcium channel blocker, and a thiazide diuretic is generally effective and well tolerated. It can be accomplished with two pills using fixed-dosed combinations.

Studies of failure of multidrug antihypertensive regimens have generally shown lack of or underuse of diuretics.[12,55,56] Most patients with resistant hypertension have inappropriate sodium and fluid retention such that use of diuretics is essential for blood pressure lowering. In most patients, use of a long-acting thiazide or thiazide-like diuretic will be most effective. In patients with underlying renal insufficiency (creatinine clearance <60 mL/min), loop diuretics may be necessary for effective volume control. Furosemide is relatively short-acting and will require dosing at least twice a day. Alternatively, loop diuretics with a longer duration of action, such as torsemide or bumetanide, can be used.

Clinical studies indicate that mineralocorticoid receptor antagonists can provide significant additional BP reduction when used in patients with BP uncontrolled on multidrug regimens. In an open-label evaluation, spironolactone 12.5 to 50 mg daily was added to regimens that included a diuretic and ACE inhibitor or ARB in all patients.[57] At 6 months' follow-up, BP was reduced by an additional 25 ± 20/12 ± 12 mm Hg (Fig. 36–2). Interestingly, the BP reduction induced by spironolactone was similar in patients with and without primary aldosteronism and was not related to baseline plasma aldosterone concentration, renin level, or 24-hour urinary aldosterone excretion. In a similar experience, amiloride 2.5 mg daily added to multidrug regimens in patients with low-renin resistant hypertension lowered BP by 31 ± 21/15 ± 11 mm Hg at 2 weeks' follow-up.[50] Further reductions in BP were observed in a subset of patients in whom the amiloride was titrated to 5 mg daily.

The studies mentioned previously indicate that mineralocorticoid receptor antagonists can be effective as add-on agents in patients with resistant hypertension. In these studies, spironolactone and amiloride were generally well tolerated,

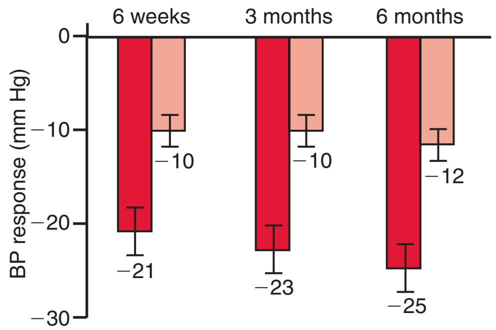

Figure 36–2 Spironolactone-induced reduction in systolic *(dark bars)* and diastolic blood pressure *(light bars)* at 6-week, 3-month, and 6-month follow-up in patients with resistant hypertension. (From Nishizaka MK, Zaman MA, Calhoun DA: Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens 2003;16: 925-30.)

although spironolactone caused breast tenderness in about 10% of the male subjects.[57] Hyperkalemia with or without acute renal insufficiency is uncommon but can occur with mineralocorticoid receptor blockade, and therefore close monitoring is indicated. The risk is increased in patients already receiving an ACE inhibitor or ARB, or both, and in patients with chronic kidney disease including the elderly and diabetics.

Adherence is generally better in patients receiving fewer pills dosed once daily. However, a cross-sectional analysis of 24-hour ambulatory BP control indicated that patients taking at least one of their hypertensive agents at bedtime had better 24-hour mean BP levels and, in particular, lower nighttime systolic and diastolic BP values.[16] The latter difference may be particularly relevant, as studies have suggested that nighttime BP levels better predict cardiovascular risk.[58,59] Twice-daily dosing of nondiuretic BP medications may improve control rates in patients with resistant hypertension. That benefit, however, would have to be reconciled with reductions in adherence that would inevitably occur with use of less convenient and potentially more expensive dosing regimens.

HYPERTENSION SPECIALIST

Studies of clinical outcomes indicate that patients with resistant hypertension do benefit from referral to a hypertension specialist.[14] In a retrospective evaluation of patients referred to a hypertension clinic, BP had declined by 18/9 mm Hg at 1 year follow-up and control rates had increased from 26% to 55%.[60] These analyses suggest that the service provided by hypertension specialty clinics including a focused review of contributing factors, exclusion of secondary causes of hypertension, and tailoring of pharmacologic therapy by an expert does serve to maximize BP control.

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Chapter 37

Hypertensive Emergencies

Radhika Katakam and Raymond R. Townsend

CHAPTER CONTENTS

INTRODUCTION

Hypertension affects millions of people in the United States and about a billion individuals worldwide. Approximately 1% of the prevalent cases of hypertension will experience a dramatic level of blood pressure (BP) elevation, receiving a clinical diagnosis of a hypertensive emergency or crisis.[1] This label applies when severe hypertension occurs with acute (or impending) target-organ damage. It is important to distinguish this from hypertensive urgency, where the BP values are high, but no target organ effect is evident and the treatment, usually as an outpatient, is instituted over days instead of minutes to hours as in the emergency situation. A more difficult distinction occurs when impressive increases in BP are present in patients with previous target organ damage (e.g., 1 year after a prior stroke). Hypertensive emergencies tend to occur more frequently in patients with previously diagnosed primary/essential hypertension who are not adherent to treatment.[2,3] This chapter discusses the definitions, epidemiology, pathophysiology, evaluation, and management of hypertensive emergencies, as well as caveats regarding the impact of potential complications on management.

DEFINITIONS

A hypertensive emergency is defined as a critical elevation in BP that results in acute or impending target organ damage. Differentiating between an emergency and an "urgency" is based on this criterion, not the extent to which the BP is increased per se.[4] Hypertensive emergencies generally require rapid reduction in BP, usually with parenteral medications given in a continuously monitored inpatient setting. Hypertensive urgencies also require medical attention, but BP can be lowered over 24 to 48 hours, most typically in a carefully followed-up outpatient setting. The rate of change in BP is particularly important in an emergency because longstanding elevations in BP are better tolerated (and typically constitute an "urgency") than rapidly climbing BP levels (over days to weeks). A rapid rise in BP can contribute significantly to target organ damage in a variety of situations: the previously normotensive patient (as in eclampsia), the patient with a process superimposed on previously well-controlled BP (such as an acute glomerulonephritis in a patient with stable prior renal function and BP control) and the patient who discontinues medications (particularly those directed against adrenergic nervous system activity, e.g., β-blockers or α_2-agonists like clonidine) and experiences a rapid loss of prior BP control. The most common causes and presentations of hypertensive emergency are shown in Table 37–1.

"Malignant" hypertension and "accelerated" hypertension are older terms used to describe critical elevations in BP. Malignant hypertension was defined by Volhard and Fahr in 1914 as a combination of severe hypertension, retinopathy with papilledema, renal insufficiency, fibrinoid necrosis of renal arterioles, and a rapidly progressive fatal clinical course.[5] The 1-year survival rate of patients presenting with these features was <30%, therefore warranting the term "malignant." The definition was later expanded to include severe hypertension accompanied by papilledema (grade IV retinopathy, according to the Keith-Wagener-Barker classification system) without concomitant renal insufficiency. Severe elevation of BP, usually marked by a diastolic BP >140 mm Hg in the presence of retinal hemorrhages and exudates but without papilledema (grade III Keith-Wagener-Barker retinopathy), was labeled "accelerated" hypertension.

EPIDEMIOLOGY AND ETIOLOGY

The exact incidence of hypertensive emergencies in the United States is not known with precision but appears to vary across different patient subpopulations. The incidence of hypertensive emergency is higher among African Americans and the elderly, occurring more often in poor, minority populations.[6] In one study hypertensive urgencies and emergencies accounted for more than one fourth of emergency department visits during a year of observation. Within these hypertensive urgency or emergency presentations, about one fourth presented as an emergency.[7]

Hypertensive emergency can occur at any age. It can affect neonates with congenital renal artery hypoplasia, children with acute glomerulonephritis, young pregnant women with eclampsia, middle-aged or older patients with treatment nonadherence, or elderly people with atherosclerotic renal artery stenosis. Such individuals typically are not accustomed to

Table 37–1 Presentations and Causes of Hypertensive Emergency

General
Abrupt increase in BP in patients with chronic hypertension
Ingestion of drugs, particularly sympathomimetic agents (e.g., cocaine, amphetamines, phencyclidine hydrochloride, lysergic acid diethylamide, diet pills, tricyclic antidepressants)
Withdrawal from antihypertensive agents (usually centrally acting agents, such as clonidine and β-antagonists)
Ingestion of tyramine-containing foods, tricyclic antidepressants, or other sympathomimetics combined with monoamine oxidase inhibitor therapy
Pheochromocytoma
Vasculitis
Autonomic hyperactivity in presence of Guillain-Barré or other spinal cord syndromes

Cardiac
Myocardial infarction and unstable angina
Acute pulmonary edema
Acute aortic dissection

Renal
Renovascular hypertension
Parenchymal renal disease (chronic) with increasing creatinine
Scleroderma renal crisis, other collagen vascular diseases
Acute glomerulonephritis
Renin-secreting tumor

Neurologic
Stroke, intracerebral hemorrhage, subarachnoid hemorrhage
Head injury
Encephalopathy

Obstetric/Gynecologic
Eclampsia

Postsurgical
Post–coronary artery bypass grafting
Post–carotid artery repair

significant elevations in BP and may present with signs and symptoms of hypertensive emergency at much lower BP levels than patients with long-standing, poorly controlled hypertension who can tolerate severe elevation in BP with less risk of target organ damage.[8]

Hypertensive emergency is more prevalent among patients with secondary hypertension, especially hypertension due to renal-artery stenosis or renal parenchymal disease than among patients with essential hypertension. Therefore, once BP is stabilized, patients presenting with hypertensive emergency should be considered for secondary causes of hypertension. However, because the prevalence of essential hypertension is so much higher than that of secondary hypertension, essential hypertension is still the most common underlying condition.

PATHOPHYSIOLOGY

The pathophysiology underlying the development of hypertensive emergency is centered on the dysregulation of pressure-dependent blood flow in critical vascular beds (especially the cerebral, cardiac, and renal circulations), which can deteriorate into frank vasculitis and ischemia. Although blood vessels normally autoregulate blood flow over a wide range of mean arterial pressure (Fig. 37–1), when the systemic pressure exceeds the autoregulatory capacity, vasoconstriction can no longer compensate and superperfusion of the tissue occurs, leading to target organ damage. In animal models of hypertensive emergency with central nervous system involvement, the arterial circulation takes on a "sausage-string" appearance from the severe vasoconstriction, with areas of intense vasoconstriction alternating with areas of vascular exhaustion and dilation (Fig. 37–2).

The flip side of this pathophysiology is equally important. Chronic hypertension results in functional and structural changes in the arterial walls, which shift the vascular autoregulatory curve to the right (see Fig. 37–1). This allows patients with hypertension to maintain normal organ perfusion by reducing or controlling the excessive blood flow that should result from the increased levels of pressure. The purposeful lowering of BP by medication during a hypertensive emergency into a range that could be considered "normal" can reduce the pressure below the autoregulatory capacity of the hypertension-adapted circulation, leading to reduced tissue perfusion and precipitating ischemia and even infarction.

Many potential factors in addition to the physical elevation of the BP itself contribute to hypertensive emergency.[9] Among locally produced factors are prostaglandins, free radicals, mitogenic and chemoattractant factors, proliferation factors, and cytokines. Endothelial damage, smooth muscle proliferation, and platelet aggregation contribute to the tissue injury seen in these patients. Among the systemic factors are increases in renin and angiotensin II, catecholamines, endothelin, and vasopressin levels. Pressure natriuresis occurs in this setting, leading to hypovolemia, which potentiates the further release of vasoconstrictor substances, such as renin and catecholamines. These factors conspire to increase BP, aggravate the endothelial damage, and ultimately lead to tissue ischemia and damage, as shown in Figure 37–3. One interesting study showed a possible association of a polymorphism of the angiotensin-converting enzyme (ACE), the DD genotype, with hypertensive emergencies in men, suggesting that there is a genetic facet to hypertensive emergency.[10] Despite the impressive array of pathogenic factors, treatment remains largely empirical (as opposed to remedying a specific mechanism) in most situations, with a limited number of reliable potent antihypertensive agents.

EVALUATION OF HYPERTENSIVE EMERGENCIES

History

The history should be brief and focused on previously diagnosed hypertension including duration, severity, and level of control. A listing of key history items is shown in Table 37–2. Less effective BP control, based on outpatient systolic BP

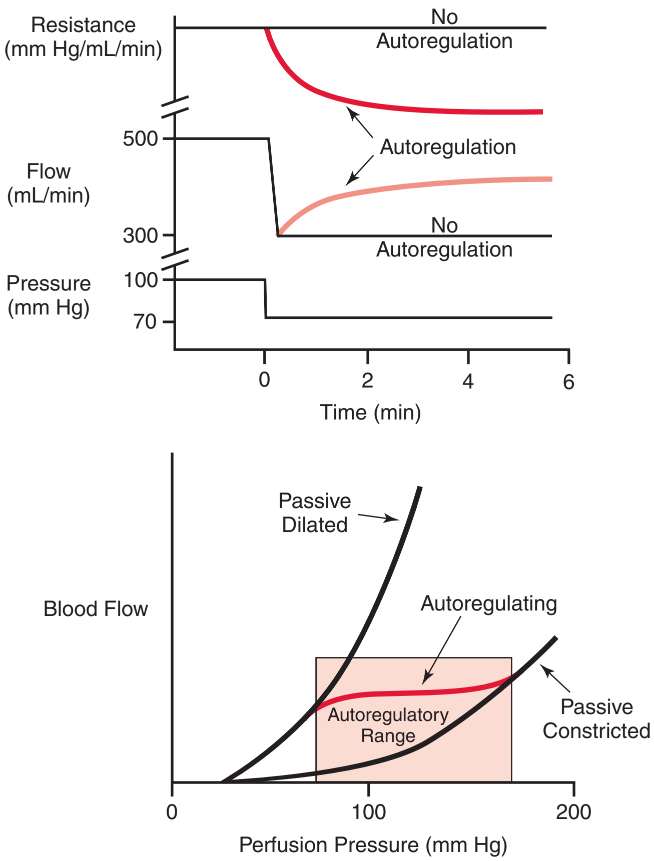

Figure 37–1 Autoregulation of blood flow *(top).* If perfusion pressure is reduced from 100 to 70 mm Hg, this causes flow to decrease initially by approximately 30%. Over the next few minutes, however, flow begins to increase back toward baseline (autoregulation—*red lines*) because vascular resistance falls. When perfusion pressure is both increased and decreased over a wide range of pressures, and the steady-state autoregulatory flow response measured, then the relationship between steady-state flow and perfusion pressure can be plotted as shown *(bottom).* The *red line* representing the autoregulatory response shows that flow changes relatively little despite a large change in perfusion pressure *(bottom).* If a vasodilator drug is infused into an organ so that its vasculature is maximally dilated and incapable of autoregulatory behavior, the curve labeled *"Passive Dilated"* is generated as perfusion pressure is changed. It is nonlinear because blood vessels passively dilate with increasing pressures, thereby reducing resistance to flow. If a vasodilator is not infused so that the organ can undergo autoregulation, then there will be a range of perfusion pressures where flow will not follow the *"Passive Dilated"* curve. The flow over a particular range of perfusion pressures (i.e., autoregulatory range) may change little as shown (e.g., as found in coronary and cerebral circulations). The *"Passive Constricted"* curve represents the pressure-flow relationship when the vasculature is maximally constricted. The *bottom panel* also shows that there is a pressure below which an organ is incapable of autoregulating its flow because it is maximally dilated. This perfusion pressure, depending on the organ, may be between 50 and 70 mm Hg. Below this perfusion pressure, blood flow decreases passively in response to further reductions in perfusion pressure. (From Klabunde RE: Cardiovascular Physiology Concepts. http://www.cvphysiology.com/blood%20flow/BF004.htm. Accessed October 4, 2005.)

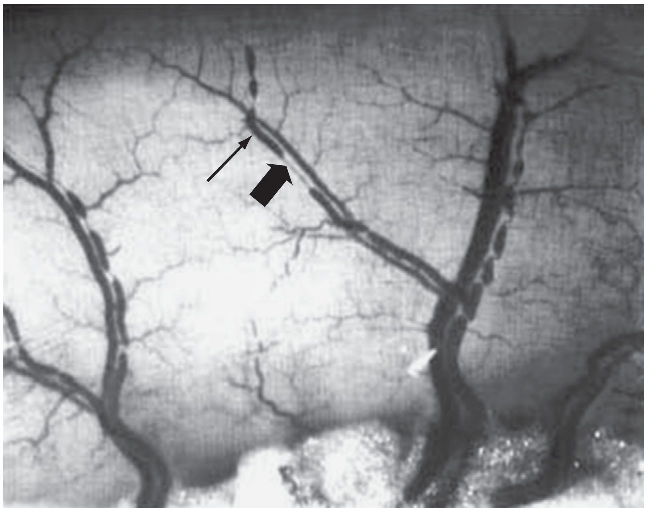

Figure 37–2 "Sausage string" appearance of alternating severe vasoconstriction *(wide arrow)* and breakthrough vasodilation *(thin arrow)* in arteriolar blood vessels (the nonconstricted vessels are venules). (From Gustafsson F: Hypertensive arteriolar necrosis revisited. Blood Press 1997;6:71-7.)

measurements, is an independent risk factor for hypertensive emergency.[11] Patients should be asked about all current medications including prescription and nonprescription drugs, their adherence to medications, and their use of recreational drugs. Symptoms related to severe elevations in BP, particularly those that suggest impending or ongoing target-organ damage, should be rapidly assessed.

Physical Examination

The physical examination should begin with several assessments of BP, using an appropriate-size cuff in both upper extremities and in a lower extremity if peripheral pulses are markedly reduced. Although an absolute level of BP is not necessary for the diagnosis of hypertensive crisis, most patients with a hypertensive emergency present with BPs at or above 200/120 mm Hg.[7,11] Pressure-induced natriuresis is a common development that may produce subtle or overt volume depletion; thus BP should be measured while the patient is both supine and standing, if possible. A checklist of key items in the examination is found in Table 37–3.

The cardiovascular examination should focus on signs of left ventricular decompensation, such as rales, a new mitral or aortic insufficiency murmur, or an S_3 gallop rhythm. The cardiovascular examination includes documentation of BP in

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Please refer to the printed publication.

Figure 37–3 Pathogenesis of organ damage from sustained hypertension. (From Nolan CR: Hypertensive crises. In Schrier RW (ed): Atlas of Diseases of the Kidney. Philadelphia, Current Medicine, 1999.)

Table 37–2 History Checklist in Hypertensive Emergency

Precipitating Factors	Evidence of Possible Target Organ Damage
Medication compliance?	Vision blurry or doubled?
Recreational drug use?	Headache (include severity/location)?
Duration of hypertension?	Nausea and vomiting?
Smoker?	Chest pain?
Current medications including OTC?	Shortness of breath?
Prior: stroke, MI, kidney disease, CHF?	Family/friends may be available re: history of confusion or ↓ cognition
	Sweating/heart racing?
	Localized weakness?

CHF, congestive heart failure; MI, myocardial infarction; OTC, over-the-counter medications, such as cough/cold preparations.

both upper extremities, particularly if thoracic aortic dissection is in the presenting differential diagnosis.

The neurologic examination should include an assessment of mental status and a funduscopic examination to detect hemorrhages, exudates, and papilledema. Hypertensive encephalopathy can reduce cognition, as well as cause focal neurologic deficits and seizure activity. Keep in mind that hypertensive encephalopathy is an exclusionary diagnosis, established after other lesions, such as stroke, subarachnoid hemorrhage, and mass lesions, have been ruled out.[4]

Initial Studies

Studies undertaken in a hypertensive emergency fall under two levels of priority. Initial studies should be limited, expedited, and used to confirm the presence of target organ compromise. The tests should be performed simultaneously with initiation of antihypertensive therapy. Subsequent testing, usually at a time when the patient is stabilized, is employed to pursue secondary causes when appropriate.

Table 37–3 Physical Examination Checklist in Hypertensive Emergency

CNS
Retinopathy/papilledema
Mental status/coma
Focal neurologic deficit(s)
Seizure
Cardiac
Rales/wheezes
Gallop rhythm
Insufficiency murmur (new)
Arrhythmia
Discrepant arm/leg pulses or BP
Renal
Flank tenderness
Edema
Bruits in abdomen

Initial studies include a urine examination, CBC with a peripheral smear, chemistry panel, ECG, and imaging when indicated. A urinalysis with microscopic examination of the urinary sediment may reveal significant proteinuria, RBCs, or cellular casts suggestive of renal parenchymal disease. The peripheral blood smear will detect the presence of a microangiopathic hemolytic anemia, which may complicate hypertensive emergency. Electrolyte abnormalities, particularly hypokalemia, reflecting aldosterone activation, occur in up to 50% of patients with hypertensive emergency. The chemistry panel may also provide evidence of renal or hepatic dysfunction, or both. The electrocardiogram identifies evidence of coronary ischemia, infarction, or left ventricular hypertrophy. A chest film may reveal pulmonary edema or a widened mediastinum, raising suspicion for an aortic dissection. When the clinical evaluation suggests cerebrovascular ischemia or hemorrhage, or if the patient is comatose, a CT scan or an MRI of the brain should be obtained immediately. In the best of circumstances, particularly in the era of electronic medical records, comparison of current results with previous findings helps to determine the chronicity of observed abnormalities.

Other testing may be necessary depending on presentations that typify less common scenarios. For example, patients presenting with significant tachycardia and sweating (signs of catecholamine excess) should be considered for plasma catecholamine and metanephrine testing, ideally before drugs with adrenergic mechanisms of action, which may cloud interpretation of plasma catecholamine and metabolite levels, are administered.

MANAGEMENT OF HYPERTENSIVE EMERGENCIES

The initial goal in management of hypertensive emergencies is progressive, controlled reduction of BP with the goal of 20% to 25% reduction in the mean arterial pressure over a period of minutes to an hour. Treatment with parenteral drugs should be administered in an ICU to control target organ damage while minimizing the risk of hypoperfusion in cerebral, coronary, and renovascular beds. The goal is *not* to lower BP to normal levels.[4,12] The asymptomatic patient who presents with severe hypertension (a diastolic BP of 130 to 140 mm Hg; i.e., an "urgency") need not be treated with parenteral drugs. In patients with major stroke, BP should not be lowered unless the etiology is hemorrhagic (see later). Aggressive treatment of BP in ischemic stroke may expand the infarction by reducing perfusion to the area of ischemia. The appropriate management of BP in ischemic stroke is still controversial due to lack of data.

A growing number of antihypertensive medications are available, and choice of drugs and selection of oral versus parenteral drugs depend on the clinical presentation and urgency of the situation. Most patients receiving parenteral therapy should have continuous arterial BP monitoring.[13] The level to which the BP should be lowered varies with the type of hypertensive crisis and other patient characteristics and should be individualized. Dosing of parenteral agents used in hypertensive crisis and the usual indications for their use are outlined in Table 37–4. Because available parenteral drugs have differential effects on the various target organs that may be involved in hypertensive crisis, the approach outlined in Figure 37–4 is recommended.

Extreme BP elevation in many clinical settings (e.g., in acute thrombotic stroke, see later) appears to have a poor outcome whether untreated or treated aggressively with parenteral antihypertensive drugs. Moreover, parenteral drug therapy not uncommonly overshoots the goal, which can worsen the situation by aggravating target organ ischemia. Thus treating hypertensive emergencies is a balancing act, with a true "risk versus benefit" circumstance in each presentation. A generous dose of frequent reappraisal is a healthy adjunct in treatment.

Cardiac Presentations

Several types of hypertensive emergencies involve the heart and aorta directly. These include coronary syndromes, pulmonary edema, and aortic dissection. In the case of suspected thoracic aortic dissection, opinions differ as to whether time-consuming radiologic tests should be completed before treatment is started or whether the clinical signs and symptoms or a noninvasive test, such as an echocardiogram, suffices to make the diagnosis before recommending surgery.[14] It is generally agreed that rapid control of the systolic BP to values <120 mm Hg, with the combined use of a vasodilator (e.g., nitroprusside) along with a β-blocker, such as esmolol, is more critical than the choice of diagnostic procedure.[15]

Nitroglycerin, nitroprusside, and nicardipine are the three drugs most commonly given (sometimes in combination) in the setting of a hypertensive emergency involving cardiac ischemia/infarction or pulmonary edema. For the latter, treatment usually includes furosemide and enalaprilat (which improve hemodynamic outcomes after pulmonary edema), followed by nitroprusside (if the BP has not yet been controlled with the previous two interventions). Intravenous nicardipine has been most commonly used after cardiac bypass or other vascular surgery (see later). Like vasodilators in general, all three drugs can cause reflex tachycardia, but their coronary arterial dilator effects usually offset the increased cardiac oxygen demand. Although nicardipine has not been widely studied in acute myocardial ischemia, there are plausible grounds for its use, along with efforts to preserve the myocardium and open the obstructed coronary artery (by thrombolytics, angioplasty, and surgery). The target BP for hypertensive emergencies involving cardiac ischemia/infarction or pulmonary edema is that which improves cardiac perfusion. A 10% to 15% reduction in BP is generally sufficient to cause a dramatic improvement in symptoms.

Coronary Syndromes

The coronary syndromes involved in hypertensive emergencies include unstable angina and acute myocardial infarction. These are usually managed with a vasodilator, especially nitroglycerin. A β-blocker, such as esmolol or labetalol, is often added for both rate control and additional BP reduction.

Heart Failure/Acute Pulmonary Edema

In acute left ventricular failure, myocardial oxygen requirements rise due to increased left ventricular volume and end-diastolic fiber length. Decreasing the workload of the failing myocardium improves heart function. These patients are treated primarily with sodium nitroprusside, a loop diuretic

such as furosemide and morphine. Vasodilators and nitroglycerin can be used alternatively. Nitroglycerin is effective in patients with acute pulmonary edema due to both ischemic and nonischemic causes.[16] Nitroprusside may be selected for patients not immediately responsive to nitrate therapy.[16] Enalaprilat is the only ACE inhibitor available for parenteral use and may be particularly useful in treating hypertensive emergencies in patients with heart failure. ACE inhibitors rapidly reduce preload and improve myocardial energy balance. Early administration of enalaprilat is effective and

Table 37–4 Parenteral Antihypertensive Agents Used in Hypertensive Emergencies

Agent	Dosing	Onset	Duration of Effect	Caveats*	Usage	Comments
ACE inhibitor						
Enalaprilat	1.25 mg	10-15 min	Up to 6 hr	Angioedema	Renal emergencies	Difficult-to-predict responses; occasional dramatic fall in BP noted
α-Blockers						
Phentolamine	1-5 mg over 1 min, repeat q 5-10 min	1 min	<10 min	Tachycardia; headache; angina	Use with suspected catecholamine excess	
β-Blockers						
Esmolol	0.2-0.5 mg/kg over 1 min; then 0.05 mg/kg for 4 min; then increase dose 0.05 mg/kg at 5 min intervals up to 0.2 mg/kg/min	1-2 min	10 min	Heart block; bronchospasm; heart failure	Postoperative presentations; coronary ischemia; thoracic aorta dissection	
Labetalol	0.5-2 mg/min; alternatively 20-80 mg IV-bolus q 5-10 min; up to 300 mg total dose	5 min	Up to 6 hr	Heart block; bronchospasm; heart failure; scalp tingling; flushing	Postoperative presentations; neurologic presentations; coronary presentations	Avoid in patients with depressed left ventricular function
Calcium-antagonist						
Nicardipine	5 mg/hr; increase by 1-2.5 mg/hr q 15 min max dose 15 mg/hr	5-10 min	1 hr, up to 4 hr	Tachycardia; headache; nausea/vomiting; phlebitis at infusion site if peripheral vein used for >24 hr	Postoperative presentations	Use with care in coronary ischemia (increase in heart rate may worsen ischemia)
Dopamine-agonist						
Fenoldopam	0.1-0.3 mcg/kg/min; increase by 0.05-0.10 mcg/kg/min q 15 min; max dose 1.6 mcg/kg/min	<5 min	30 min	Tachycardia; headache; flushing	Renal presentations (does not impair GFR); used as alternative to nitroprusside, especially postoperatively	Use with caution if glaucoma suspected; may reduce K^+; tends to be less effective after 48 hr

Continued

Table 37–4 Parenteral Antihypertensive Agents Used in Hypertensive Emergencies—cont'd

Agent	Dosing	Onset	Duration of Effect	Caveats*	Usage	Comments
Vasodilators						
Diazoxide	50-150 mg bolus; 15-30 mg/min continuous IV	2-5 min	3-12 hr	Tachycardia; angina; nausea; increased glucose		Used rarely; not used for coronary presentations or with aortic dissection due to heart rate increase
Hydralazine	10-20 mg @ 1 mg/min	10-20 min	3-8 hr	Tachycardia; angina; flushing; rash; headache	Eclampsia	Increased heart rate limits value in cardiac presentations; increased intracranial pressure limits value in neurologic presentations
Nitroglycerin	5-100 mcg/min (titrate q 5 min)	2-5 min	3-5 min	Headache; nausea and vomiting	Acute MI; pulmonary edema; cocaine use with coronary ischemia	Headache may be severe
Nitroprusside	0.3-10 mcg/kg/min	<1min	1-2 min	Headache; nausea and vomiting; thiocyanate toxicity	Encephalopathy; pulmonary edema; most hypertensive emergencies are managed with this drug	Cyanide and thiocyanate toxicity more likely with reduced renal function or rate >2 mcg/kg/min or both
Ganglionic Blocker						
Trimethaphan	0.5 mg/min to 5 mg/min; max dose 6 mg/min	1-5 min	5-10 min	Urine retention; ileus; respiratory arrest	Aortic dissection	Uncommonly used because of frequent instability in BP effect; mostly supplanted by nitroprusside
Miscellaneous						
Magnesium-SO_4	1 g/min up to 4 g (IV)	<1 min	30 min	Sweating, flushing, respiratory and cardiac	Eclampsia	Intramuscular has slower onset and lasts longer; goal serum concentration is 4-6 mEq/L

All agents in this table have "hypotension" as an adverse effect.

well tolerated in acute pulmonary edema.[17] A loop diuretic is usually administered along with these agents. A meta-analysis has shown no significant difference in efficacy of ACE inhibitors versus diuretics or β-blockers in hypertensive patients with heart failure.[18]

Neurologic Presentations

In patients with elevated BP and neurologic abnormalities, examination of the fundus by direct ophthalmoscopy can be helpful in making a proper diagnosis. The finding of

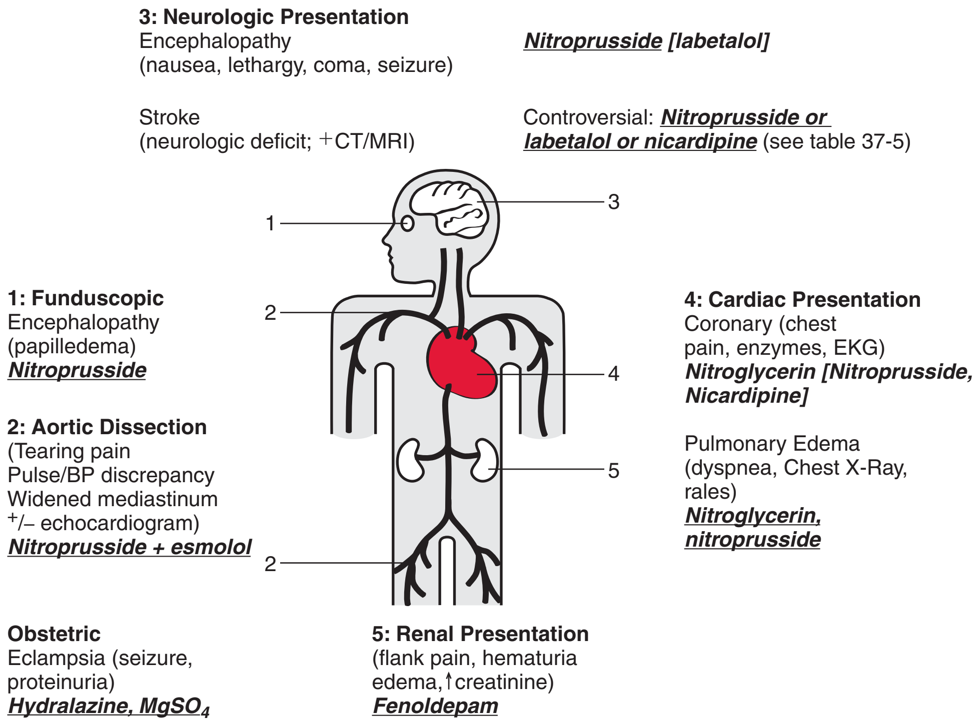

Figure 37–4 Classification of hypertensive emergencies by presentation with key findings in parentheses and initial therapy recommendations in bold, underlined, italic text with secondary agents within brackets.

papilledema or new hemorrhages or exudates is diagnostic of hypertensive emergency, and these patients often manifest hypertensive encephalopathy. The neurologic examination should document the extent and severity of any focal neurological defects because these may change with time or treatment, or both, possibly altering BP management.

The various neurologic emergencies can be difficult to distinguish. Encephalopathy from hypertension is typically a diagnosis of exclusion. Stroke (hemorrhagic and thrombotic) is typically diagnosed by sustained focal neurologic signs on physical examination and a confirmatory CT or MRI scan of the brain. Subarachnoid hemorrhage may be evident on CT or MRI but may also require a lumbar puncture. The patient with BP elevation following head trauma, known as Cushing's reflex, will usually have a trauma history and the physical findings of head trauma to aid the diagnosis. In both acute stroke and the hypertension after head trauma, the BP goal is controversial. Moreover, the management of these sundry conditions is somewhat different. Nitroprusside is still the drug typically chosen for encephalopathy (see later) and is used in many other acute hypertensive conditions. Nimodipine has antihypertensive and anti-ischemic effects and is approved for use in subarachnoid hemorrhage,[18,18a] but it did not show benefit when used early in thrombotic stroke.[19]

Encephalopathy

Hypertensive encephalopathy is a syndrome consisting of a sudden elevation of arterial pressure usually preceded by severe headache and followed by convulsions or coma. Other clinical features include nausea, vomiting, visual disturbances, and a change in mental status. Encephalopathy is accompanied by a severe increase in vascular resistance, and because clinical experience has demonstrated clearing of the sensorium, cessation of convulsions, and release of vasoconstriction following reduction of BP, BP should be lowered promptly.[20]

Drugs that have few or no central nervous system side effects should be used, and agents such as clonidine, guanfacine, methyldopa, and reserpine should be avoided. Diazoxide can decrease cerebral blood flow, so it should also be avoided. Nitroprusside, which may actually increase intracranial pressure, continues to be the agent of choice for treatment of hypertensive encephalopathy.[4] Goal BP reduction is approximately 25% below starting values, achieved over about an hour while maintaining a diastolic BP above 100 mm Hg.

Stroke

Stroke is especially difficult to manage with parenteral antihypertensive therapy, in part because lowering BP in acute *nonhemorrhagic* stroke patients without either hypertensive encephalopathy or a cardiovascular indication that requires immediate reduction of BP may cause harm[21] and is not recommended by guidelines.[22] Lowering the BP in patients with cerebral ischemia may reduce cerebral blood flow. Because cerebral autoregulation is often impaired in these patients, this may result in further ischemic injury. The common practice of "normalizing" BP is thus potentially dangerous. Some experts advise that unless systolic BP exceeds 220 mm Hg or diastolic exceeds 120 mm Hg, it should not be lowered, except if thrombolytic therapy is planned (Table 37–5). Parenteral agents, such as labetalol, that are easily titrated and that have minimal vasodilator effects on cerebral blood vessels are preferred. Sublingual use of a calcium antagonist, such as nifedipine, should be avoided because of rapid absorption and a secondary precipitous decline in BP.[22] As noted earlier, centrally acting agents should be avoided because of their potential to interfere with mental status.

Table 37–5 Approach to Elevated Blood Pressure in Acute Ischemic Stroke

Clinical Situation	Recommendation
A. Not eligible for thrombolytic therapy Systolic BP <220 mm Hg; diastolic BP <120 mm Hg	Observe BP unless there is other end organ involvement, such as aortic dissection, renal failure, or acute myocardial infarction, which would mandate emergency treatment
Systolic BP >220 mm Hg or diastolic BP 121-140 mm Hg	Labetalol 10-20 mg IV over 1-2 min; may repeat or double every 10 min to a maximum dose of 300 mg **OR** nicardipine 5 mg/hr IV infusion as initial dose; titrate to desired effect by increasing by 2.5 mg/hr every 5 min to maximum of 15 mg/hr (target 10-15% reduction)
Diastolic BP >140 mm Hg	Sodium nitroprusside 0.5 mcg/kg/min IV with continuous BP monitoring (target 10-15% reduction)
B. Patient eligible for intravenous rt-PA	If systolic BP >185 mm Hg or diastolic BP >110 mm Hg, intravenous labetalol, 10-20 mg over 1-2 min; may repeat × 1 or 1-2 inches of nitropaste; if BP is not reduced and maintained at desired levels (<185 mm Hg systolic BP and <110 mm Hg diastolic BP), do not administer rt-PA

From Adams HP Jr, Adams RJ, Brott T, et al: Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003;34:1056-83.

Intracerebral Hemorrhage

Patients with hypertensive intracerebral hemorrhage who present with marked elevation of BP (defined as a mean arterial pressure of >145 mm Hg) have been shown to have higher mortality and more severe morbidity than those with lesser degrees of BP elevation.[23] With radiologic evidence of a major intracerebral bleed, *cautious* lowering of BP, if systolic BP >200 mm Hg or diastolic BP >120 mm Hg, is generally suggested and supported by studies that showed that a *rapid* decline in BP within the first 24 hours after an intracerebral hemorrhage was associated with an increased mortality.[24] Further, in patients with intracerebral hemorrhage, the value of early antihypertensive therapy in preventing rebleeding or reducing vasogenic edema has not been demonstrated.

Subarachnoid Hemorrhage

As with stroke, BP lowering here is controversial. Nimodipine (orally) has been approved with the goal of preventing reflex vasospasm (not blood pressure lowering per se) in the period following the initial bleeding episode. It is considered reasonable to lower blood pressure in subarachnoid hemorrhage, particularly when the systolic blood pressure is substantially elevated (i.e., >160 mm Hg) and thus the risk of bleeding and mortality is increased,[25] However, there is no consensus as to a goal level or recommended rapidity of reduction.

Renal Presentations

Microscopic hematuria or a worsening of renal function, or both, characterize kidney involvement in hypertensive emergency. Gross hematuria is less common than microscopic hematuria, but its presence should trigger a urologic evaluation once blood pressure is stabilized. Acute renal failure can both cause and result from elevated blood pressure, and severe hypertension often accompanies acute renal failure. Consequently, a urinalysis should be performed and serum creatinine measured in the initial evaluation of patients with extreme blood pressure increases.

Not uncommonly, and in our experience more often in African-American patients, successful treatment of hypertensive emergencies with reduced renal function results in further renal function impairment. This (usually) temporary worsening of renal function can occur even when the blood pressure is correctly titrated downward in a controlled gradual fashion and can occasionally result in the need for acute dialysis. When this happens, most patients can usually stop dialysis during long-term follow-up if blood pressure remains well-controlled.[26,27] Therapy in renal presentations should reduce systemic vascular resistance without diminishing renal blood flow. The dopamine-agonist fenoldopam and the calcium channel blocker nicardipine are effective in this situation. Although nitroprusside is also effective, it carries a risk of cyanide and thiocyanate toxicity. When compared with nitroprusside, fenoldopam improves natriuresis and creatinine clearance in patients with elevated blood pressure and impaired renal function.[28]

Catecholaminergic Presentations

Hypertensive emergencies from an excess of catecholamines are associated with pheochromocytoma; monoamine oxidase (MAO) inhibitor therapy; abrupt withdrawal of chronic anti-adrenergic antihypertensive therapy; and the use of drugs, such as cocaine, phencyclidine hydrochloride (PCP), lysergic acid diethylamide (LSD), and amphetamines. The typical triad of headache, sweating, and rapid heart rate along with severe hypertension are the classic characteristics of pheochromocytoma. Physical examination of the skin may provide additional clues (e.g., neurofibromas, port wine stains, café-au-lait spots) to the diagnosis. In some patients the presentation is overwhelmingly cardiac, with severe hypertension, heart failure, and lactic acidosis dominating the picture. Patients receiving MAO inhibitors have generally

been warned that taking these drugs and ingesting tyramine-containing foods can prompt a hypertensive emergency. However, incomplete or inaccurate food labels and dietary or pharmacologic indiscretions (e.g., tricyclic antidepressant use) still occur. A thorough medication history is the only way to make a diagnosis.

Abrupt withdrawal of anti-adrenergic antihypertensive agents, such as clonidine, is more likely to result in a true hypertensive emergency when coronary disease is also present. When clonidine is abruptly discontinued (especially at high dosages) or rapidly tapered, a syndrome consisting of nausea, palpitation, anxiety, sweating, nervousness, and headache, along with marked elevation of the blood pressure, has been noted. Symptoms of clonidine withdrawal can be relieved by reinstituting the clonidine regimen. Abrupt withdrawal from β-blocker therapy may also lead to a syndrome suggestive of sympathetic overactivity. Importantly, the possibility of precipitating angina, myocardial infarction, or sudden death in patients with coronary disease is the major reason to treat this situation with parenteral, as well as oral, therapy. Cocaine may be inhaled, injected, or snorted intranasally. It elevates blood pressure by preventing synaptic catecholamine reuptake with spillover.[29] Cocaine and its metabolites are detectable on a drug screen for up to 36 hours after administration. A syndrome of catecholamine excess can result from spinal cord injury or severe head injury.

In general, catecholaminergic presentations are managed using a direct vasodilator (e.g., phentolamine, nitroprusside) or a combination α-blocker and β-blocker agent (e.g., labetalol). β-Blockers can potentially exacerbate hypertension in patients with catecholamine excess and are better used when adequate vasodilation or α-receptor blockade, or both, are achieved.[12] Treatment of hypertensive emergencies due to pheochromocytoma usually begins with an intravenous α-blocker (phentolamine). A β-blocker is added only if necessary. In the case of MAO inhibitor ingestion, there is a paucity of literature to guide treatment, but the mechanism of hypertension argues that an α-blocker, such as phentolamine, is reasonable to use.[30] Severely elevated BPs due to abrupt withdrawal of anti-adrenergic antihypertensive agents, such as clonidine or β-blockers, are managed by restarting therapy; often a single dose is adequate to produce significant improvement. Treatment of hypertensive emergencies due to cocaine abuse is based on the presence or absence of overt coronary ischemia (about 1 in 20 subjects presenting with cocaine toxicity has acute coronary ischemia[29]). Oxygen, nitrates, verapamil, aspirin, and benzodiazepines are preferred in coronary presentations of cocaine intoxication. Either labetalol or phentolamine is useful when the main issue is blood pressure control.

Thoracic Aortic Dissection Presentations

The most common presenting symptom in thoracic aortic dissection is a severe sharp, tearing, or ripping type of pain (>95%). Most patients say that pain is abrupt in onset and either located in the chest and back (with aortic arch dissections 70%) or the back and abdomen (with dissections of the descending aorta 50% to 65%). Significant differences in brachial artery pressure (right vs. left arm; arm vs. leg); new pulse deficits; a new aortic regurgitation murmur; and Marfan appearance (tall, long limbs, scoliosis, eye findings) are features suggestive of aortic dissection.

Whether or not surgery is undertaken, each acute thoracic aorta dissection patient is a candidate for medical therapy. Surgery is typically undertaken for type A dissections, which involve the aortic arch.[31] Dissections involving only the aorta distal to the left subclavian artery are typically managed medically unless a critical ischemic complication (e.g., a bowel infarction) intervenes.

BP control to a target systolic pressure of 110 mm Hg can be achieved with an intravenous β-blocker, and the short-acting agent esmolol is often used[32] in combination with vasodilating drugs, such as sodium nitroprusside or ACE inhibitors. Intravenous verapamil or diltiazem may also be used, especially if β-blockers are contraindicated. Nitroprusside is usually initiated to reduce the blood pressure quickly and uniformly, with upward titration to achieve the systolic blood pressure goal of <110 mm Hg. Because nitroprusside does not reduce (and may increase) the shearing force of the blood, it should be accompanied by β-blockade.

Obstetric Presentations (Eclampsia)

Obstetric hypertensive emergencies are usually diagnosed at lower BP levels than in nonpregnant patients. Preeclampsia presents with elevated BP (systolic BP of ≥140 mm Hg and diastolic BP of ≥90 mm Hg), typically occurring after the 20th week of gestation in a woman whose blood pressure has previously been normal, and proteinuria, with excretion of 0.3 g or more in a 24-hour period. A woman with preeclampsia who has new-onset grand mal seizures is considered to have eclampsia. Risk factors for the development of eclampsia include preexisting hypertension and renal disease.[33]

Many antihypertensive drugs are contraindicated in pregnancy. Nitroprusside is metabolized to cyanide, which is toxic to the fetus. ACE inhibitors (and angiotensin receptor blockers) carry black-box warnings indicating that they are contraindicated in the second and third trimesters of pregnancy because of adverse effects on the fetus. The ganglion-blocking drug trimethaphan should be avoided because of the risk of meconium ileus. Although definitive therapy is delivery of the fetus, the BP should also be reduced to prevent neurologic, cardiac, and renal damage in the mother. Magnesium sulfate is the standard of therapy for prophylaxis and treatment of seizure activity, with a loading dose of 4 to 6 g in 100 mL dextrose 0.25 saline solution over 15 to 20 min.[34] Because magnesium sulfate has a cerebral vasodilator effect, one explanation for its antieclamptic action is that it decreases ischemia by reducing cerebral vasospasm.[35] Although other antihypertensive drugs may be equally effective in reducing blood pressure, the agent of choice is hydralazine, which has a long record of safety. Nifedipine and β-blockers (particularly labetalol) can be added later if necessary. Delivery of the infant typically lowers the mother's BP. Please see Chapter 39 for a more comprehensive discussion of the management of hypertension in pregnancy.

Hemorrhage and Post-Vascular-Surgery Presentations

Bleeding that does not respond to local measures, such as direct pressure, occurring in association with severe blood pressure elevation, can be a hypertensive emergency. Common bleeding sites are the nose, urinary tract, and surgical sites,

especially in the post-vascular-surgery period. The bleeding is usually witnessed by the patient, often inducing substantial anxiety, thus contributing to the blood pressure elevation. Consequently, it may be wise to both lower the blood pressure acutely and provide judicious anxiolytic therapy.

In postoperative situations, particularly after coronary artery bypass graft (CABG) surgery or carotid endarterectomy, bleeding from suture lines is a significant concern. In the post-CABG patient nitroglycerin is an effective and rational way to manage blood pressure. Post–carotid endarterectomy patients frequently suffer from labile blood pressures that can last for days. One possible cause is disruption of the baroreceptor reflex from trauma or damage to the carotid sinus or vagus nerve during surgery. Hypertension in this period can lead to the "hyperperfusion syndrome" and neck hematoma, particularly in patients undergoing percutaneous stenting procedures. This hyperperfusion syndrome is seen in patients with high-grade carotid artery stenosis, especially with bilateral disease, presumably because of a maximal dilation of the arteries distal to the stenosis to maintain perfusion in a situation where autoregulatory mechanisms are lost. After the stenosis is relieved by surgery or stenting, there is hyperperfusion of that hemisphere, with increased risk of intracranial hemorrhage and seizures.[36]

CAVEATS TO THERAPY IN HYPERTENSIVE EMERGENCY CARE

- When undertaking parenteral therapy in a hypertensive emergency, establish how quickly and by how much you want to see the blood pressure reduced. Be prepared to back off when the clinical situation worsens, particularly from a cognition standpoint.
- Patients with a hypertensive emergency (other than acute pulmonary edema) tend to be volume depleted; thus there is no role for "routine" administration of diuretics. On the other hand, with effective BP reduction, after a day or two there is often evidence of salt and water retention, which jeopardizes continued BP control. At that point diuretic therapy tends to be more rational and effective.
- In patients presenting with presumed catecholamine excess, the recommended approaches are usually effective in lowering BP within minutes. Thus, if a poor response is noted, other diagnoses (and treatment) should be considered.
- One key element in prevention of future episodes is adequate care and follow-up after hospitalization.

CONCLUSION

Hypertensive emergency is a relatively uncommon complication, usually occurring in the setting of long-standing hypertension. Patients with hypertensive emergency typically require immediate reduction in BP to interrupt ongoing or prevent impending target-organ damage. A variety of antihypertensive medications are available for hypertensive emergencies; the choice of drug depends on the type of emergency and the individual patient. Parenteral agents should be used initially. When BP has been stabilized for 24 hours, parenteral antihypertensive medications can be gradually changed over to oral medications. Consideration of secondary causes of hypertension is recommended, particularly in patients without a clear precipitating cause of the hypertensive emergency (e.g., medication nonadherence, an intervening comorbidity, or intercurrent sympathomimetic drug use).

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Chapter 38

The Metabolic Syndrome

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CHAPTER CONTENTS

The metabolic syndrome is linked primarily to the excess body weight and obesity that are affecting a major proportion of the American population and creating substantial health, social, and economic burdens. At least part of this problem stems from an increasing consumption of high-calorie foods and a reduction in physical activity, particularly in children. Typically, excess weight leads to a cardiovascular metabolic syndrome that is characterized by insulin resistance, lipid abnormalities, high blood pressure (BP), and increased abdominal girth. This syndrome directly increases the risks of cardiovascular and renal events; moreover, it often leads to type 2 diabetes, which sharply amplifies the probability of adverse outcomes. It is now recognized that increased fat mass itself can be a major driver of these events. Fat cells produce adipokines, factors that have inflammatory, proliferative, and prothrombotic effects. The renin-angiotensin-aldosterone system is also stimulated by these cells. The importance of free fatty acids—independent of the state of obesity—is now recognized. Their metabolites within skeletal muscle and liver cells appear to inhibit glucose transport and thereby create insulin resistance. Obesity, however, cannot be blamed for all cardiovascular disease. Interesting data show strong familial trends in the development of the cardiovascular metabolic syndrome. This suggests the possibility of genetic causes, but environmental factors cannot be ruled out. Dealing with obesity will require public policies that will affect dietary and physical activity measures in schools, community institutions, and the workplace. Innovative drugs and minimally invasive surgeries may be partial answers for people with more severe forms of obesity. In addition, new drugs directed at the individual risk factors that comprise the metabolic syndrome and at preventing progression to clinical diabetes must be considered in patients with this condition.

BACKGROUND

The metabolic syndrome can be considered as an intermediate clinical stage, having its origins in excessive calorie intake and its consequences in cardiovascular disease. Many people who are obese or overweight experience metabolic changes that increase their risk of adverse cardiovascular and renal outcomes. In particular, there is evidence for such findings as insulin resistance, lipid abnormalities, increased BP, and microalbuminuria. These are part of a series of abnormalities that constitute what is now usually referred to as the *metabolic* or the *cardiovascular-metabolic syndrome.*

This syndrome, in turn, often leads to cardiovascular events and type 2 diabetes mellitus. Still, despite our preoccupation with obesity as the major factor in this sequence of events, we should not forget that many patients with cardiovascular and renal disease are not overweight. If we are to take a constructive view of the problem of cardiovascular disease that is linked to excess body weight, we can make the argument that this situation potentially can be remedied by a concerted effort of patients, clinicians, and society. An excellent review of the public health implications of this problem was published by senior scientists at the U.S. Centers for Disease Control.[1]

The Breadth of the Problem

Clinicians are understandably both intrigued and frustrated by the current epidemic of obesity. Although many health care practitioners work hard to support and advise their patients in efforts to counter this problem, many external forces work against them. The lay public is already fully aware of the problem of excess body weight and its serious consequences. The print and broadcast media, elected officials, and policy makers have all clearly recognized the medical and economic threats that are posed by this phenomenon. This chapter does not discuss these social and political issues. Clearly, though, they are deeply embedded into our contemporary lifestyle. We live in a world where physical activity for all ages, but particularly for children, has been largely replaced by virtual activity. For the present generation, the computer and other electronic devices have become the main focus of attention. The ready availability of high-calorie and high-fat foods, cleverly and aggressively promoted by their manufacturers, provides seemingly irresistible temptations, again especially affecting children. The health care professions alone clearly cannot solve these problems. Solutions will depend as much on changes in public policy and educational activities as on the efforts of clinicians.

DEFINING AND EXPLAINING OBESITY

The National Institutes of Health has based its classification of body weight on the concept of body mass index (BMI), which is derived by dividing body weight by the square of height.[2] A classification based on a measurement such as this inevitably is somewhat arbitrary and is designed simply to provide an approximate guide for identifying people at differing levels of risk for cardiovascular events. A normal or acceptable BMI is lower than 25 kg/m^2, overweight is between 25 and 29.9 kg/m^2, and obesity is 30 kg/m^2 or higher. Some critics have actually argued that these definitions are too generous, particularly as an optimal cardiovascular prognosis appears to be associated with a BMI of approximately 21 kg/m^2.[3] Realistically, however, if such a low value were to be set as a desirable target, only a small fraction of present-day Americans could meet it.

Another shortcoming of using BMI for classification purposes is that it does not adequately address the physical distribution of excess fat tissue in the body. For the same BMI, a person with predominantly abdominal obesity is at greater risk of serious cardiovascular events than a person whose obesity is chiefly found below the hips. For that reason, clinicians have also directed their attention to measurements of the hips, the waist (the greatest circumference around the central abdomen), and the ratio of the waist-to-hip measurements. In fact, this approach has been used (in preference to BMI) as a criterion for establishing the metabolic syndrome (see later). But whatever methods are used, the prevalence of health-threatening excess body weight and obesity is remarkably high.[4]

Table 38–1 Factors Contributing to Obesity

Dietary
Excess consumption
Calorie-dense foods
High-fat foods
Relatively higher price of healthier, fresh produce
Exposure to advertising for fast foods, beer, and high-calorie products
Eating disorders
Behavioral
Inadequate regular exercise
Low physical activity at work
Low recreational physical activity, lack of facilities
Childcare or domestic arrangements that limit opportunities for spontaneous play by children
Excessive time with computers and television
Medical
Disabilities that impair physical activity
Pregnancy
Certain antidepressant or antipsychotic drugs
Rare endocrine and genetic disorders
Children of mothers who were diabetic or ate excessively during pregnancy

Looking at Causes

Factors that contribute to excess weight are listed in Table 38–1. In essence, the explanation for obesity in most people is that they consume more calories than they expend. It is also easy to see that two ongoing trends in our society can so readily explain the overall problem: (1) We are eating progressively larger portions of the fast foods and beverages (especially beer) that are so attractively and relentlessly advertised on television or in popular magazines; and (2), progressively more time is being spent with computers and televisions, as compared with planned or spontaneous pursuits involving physical activity—particularly as far as children are concerned. It is clear throughout our society what these issues are, but we have been ineffective at dealing with them.

Committees of experts asked to give advice on this matter have recommended that people spend at least 30 minutes involved in energy-consuming physical activities on a daily basis.[5] But there is little, if any, evidence that such recommendations on exercise and dietary changes have had any impact on the body weight of Americans. Clearly, a more thoughtful plan of education, backed up by detailed assessments of the many components that comprise the organization of life in our communities, would be more effective overall than general exhortations to exercise more and eat less. That is not to say that we do not already have a number of organized programs targeted at after-school and recreational activities for children,[6-8] as well as programs targeted at adults with major weight problems.[9,10] Some of these innovative programs have shown promising results, but clearly a major impact across the population will require public policies that comprehensively affect schools, public facilities, places of employment, and—hopefully in a voluntary fashion—the participation of the commercial food industry.

Impact of Excess Body Weight: A Changing Pattern

Obesity in the United States causes a substantial number of excess deaths each year.[11] It can be noted, though, that obesity-related mortality rates are now lower than they were about 30 years ago.[12] Presumably this change reflects an improvement in medical management of the risk factors associated with obesity. Even so, one assessment of this situation concluded that unless the obesity problem can be dealt with decisively, today's young adults and children are destined to live shorter and less healthy lives than their parents,[13] thus overturning previous trends to greater longevity.

An unexpected observation of weight-related secular trends is that overweight people (BMIs between 25 and 29.9) have mortality rates that are not only lower than in the obese, but are also lower than in lean individuals.[12] This finding has not gone unnoticed, and the lay press has even wondered whether the antiobesity establishment, which includes commercial weight-loss centers, dietary food makers, pharmaceutical companies, diet book publishers, and physicians, have been guilty of self-interest in drawing excessive attention to this issue.[14] However, changes in medical practice, particularly in dealing with cardiovascular risk factors, could at least partly explain this apparent paradox. Indeed, with the exception of type 2 diabetes, there has been a marked reduction in the prevalence of clinically manifest risk factors including high BP and hypercholesterolemia during the past 40 years.[15] This trend has been linked to increased prescribing of antihypertensive and lipid-lowering medications,[15] which, beyond their

intended therapeutic effects in countering what otherwise would have been a worsening of these findings, could additionally have pleiotropic actions that might further enhance prognosis. It is also possible that other mechanisms, discussed later in the context of obesity and hypertension, could further explain better-than-expected mortality outcomes in obese individuals.

Further Consequences

Problems of high body weight are associated with a wide range of morbidities. These include not only cardiovascular risk factors like hypertension or lipid abnormalities, but also such conditions as osteoarthritis and cholelithiasis.[16,17] Clearly, the metabolic syndrome, which so often results from obesity and predisposes to the high-risk condition of type 2 diabetes, is a serious concern. A list of common conditions that are at least partly related to obesity is given in Table 38–2.

Obesity-related problems are not always confined to patients who are seen in cardiovascular or other specialty practices. Nor are problems of weight confined to adults. Indeed, obese children are very much at risk of developing the metabolic syndrome,[18] and type 2 diabetes has now become commonly diagnosed in adolescents. In a study of youngsters ages 4 to 20, it was shown that increasing levels of obesity were associated with increases in blood concentrations of glucose, insulin, and triglycerides, together with reduced blood concentrations of high-density lipoprotein (HDL) cholesterol.[18] Along with evidence for glucose intolerance and insulin resistance, there was also an increase in systolic blood pressure. Remarkably, this study showed that whereas 50% of severely obese children and 39% of moderately obese children satisfied diagnostic criteria for the metabolic syndrome, there was no evidence for this syndrome in children with normal or only moderately increased body weight.[18]

Beyond its clinical and societal impact, obesity also produces strong adverse economic consequences. Experts in outcomes research, using data from the National Health and Nutrition Examination Survey III, have noted that during the decade running from approximately 1990 to 2000 there was a 44% increase in obesity in the United States and that this problem affected almost 30% of all people in regular employment.[19] Not surprisingly, obese workers were found to have work limitations at least twice as commonly as normal weight workers, to be four times as likely to have hypertension, three times as likely to have type 2 diabetes, and several-fold more likely to have the metabolic syndrome.[19] Again, quite apart from the human burden of these problems, it is easy to see the disruptive and costly effect of obesity on the economy.

It has been estimated that the cost of lost productivity and the direct cost of caring for the morbidities and limitations of obese and overweight persons total approximately $100 billion each year.[20] If we consider some of the noncardiovascular medical consequences of obesity (see Table 38–2), it could be argued that the true costs of this condition are even greater.

Table 38–2 Conditions That Can Result from Obesity

Type 2 diabetes mellitus
Dyslipidemia
Coronary heart disease
Hypertension
Atrial fibrillation
Stroke
Obstructive sleep apnea
Cholelithiasis
Postmenopausal breast cancer
Endometrial carcinoma
Prostate cancer
Osteoarthritis

How Common Is Excess Weight?

The worsening picture regarding the prevalence of obesity is shown in Figure 38–1. These data show an inexorable increase in obesity from the early 1960s to 2000, rising from approximately 14% to 31% of the adult population during that time. Worse, the rate of rise during that 40-year period actually accelerated from the mid 1970s until about 1990 and appeared to increase even faster after that. The curve for Americans who are considered overweight (BMIs between 25 and 29.9) follows a similar contour; however, because this number had already reached 45% in 1960, the relative increase to 65% by 2000 does not seem quite so dramatic. These findings indicate that barely one third of Americans currently has an acceptable body weight. More detailed information from the same source[1] suggests that, in general, obesity is more of a problem in the Eastern than in the Western states and that it is somewhat more prevalent among African Americans, particularly women, than whites. As discussed earlier, school children are also increasingly overweight or obese: This is true not only in the United States[21,22] but also in Great Britain[23] and Asia,[24,25] where presumably similar behavioral factors are at work.

THE LINK BETWEEN EXCESS BODY WEIGHT AND THE CARDIOVASCULAR METABOLIC SYNDROME

The presence of obesity, even in relatively young adults with no history of previous cardiovascular events, is predictive of metabolic, cardiovascular, and renal abnormalities.[26] Clinical

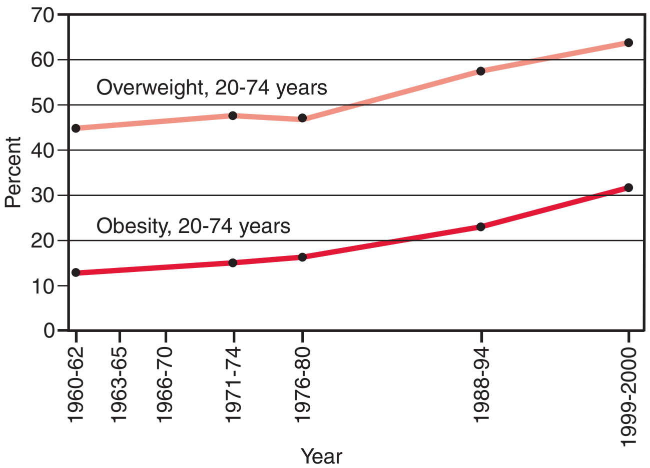

Figure 38–1 Overweight and obesity by age: United States, 1960-2000. (From Trends in Health of Americans. Hyattsville, Md, National Center for Health Statistics, 2003.)

findings in a cohort of individuals we identified by community screening, divided into those who were either obese or nonobese, and either hypertensive or normotensive, are shown in Table 38–3. Clearly, LDL-cholesterol levels are higher and HDL-cholesterol levels are lower in obese individuals, regardless of whether or not they are hypertensive. Triglyceride levels are higher in obese hypertensives (though not in obese normotensives) when compared with nonobese individuals. Interestingly, insulin concentrations are significantly higher in obese persons, either hypertensive or normotensive, than in lean individuals; in fact, insulin levels in lean hypertensives are lower than in normotensive obese individuals, indicating the clear importance of obesity per se as a determinant of early insulin resistance. Therefore, key findings associated with the metabolic syndrome (see later for definitions) are found readily during routine observations in the community.[26]

In the same cohort of subjects (see Table 38–3), obesity and hypertension were associated with a relative increase in echocardiographically measured left ventricular muscle mass index.[26] Because this measurement was factored by body size, the increase in left ventricular mass in obese persons is a real and potentially important finding. One piece of good news for obese people, as shown in Table 38–3, is that their total arterial compliance (as shown by the SV/PP measurement) is actually higher than in lean hypertensives, indicating that increased arterial stiffness—at least as measured by this technique—is not a major issue in obesity.

Renal Effects

Two findings regarding renal function in obese persons are interesting: (1) Creatinine clearance is higher in obese persons, regardless of whether they are hypertensive or not; and (2) the albumin excretion rate is also higher in obese people, again independent of blood pressure status. Obesity is known to affect renal function, in particular increasing sodium reabsorption,[27,28] an action probably mediated by increased renal sympathetic activity.[29] Whether these sympathetic mechanisms also cause the hyperfiltration we observed in obese patients is unknown,[26] although this phenomenon has also been observed by other investigators.[30] This finding may help explain the microalbuminuria found in obese subjects, one of the important diagnostic criteria for the metabolic syndrome as defined by the World Health Organization. Finally, the increased sodium reabsorption[27,28] found in obesity could also contribute to the increased plasma volume and cardiac output—probably important factors in increasing systolic blood pressure—that are typical of these individuals.[31]

Evidence for similar changes in children exists. A study performed in children with an average age of 13 showed that urinary albumin excretion was significantly higher in obese youngsters than in those with normal weight, and that in the obese children the albuminuria correlated with measurements of fasting blood insulin and cholesterol concentrations.[32] The authors of that study concluded that even at a young age, the presence of obesity might lead to early dysfunction of the renal glomerulus and tubule.

Early in the process of obesity, either in children or in younger adults who have not yet experienced cardiovascular or renal events, there are already important clinical manifestations associated with obesity. These include metabolic findings indicative of insulin resistance and lipid abnormalities, as well as early changes in cardiovascular and renal structure and function. Moreover, increased plasma volume and possibly some regional changes in sympathetic activity make these patients more vulnerable to adverse outcomes. How obesity leads to these findings is not clear, but there is growing interest in the possibility that the adipose cell itself may be an important mediator of some of these major clinical attributes of obesity.

The Fat Cell: A Key Biologic Contributor

A variety of mechanisms link obesity and adiposity to insulin resistance, diabetes, and cardiovascular risk. Traditionally, fat cells were seen primarily as storehouses for energy, chiefly in the form of triglycerides, but it is now apparent that adipose tissue can function as an endocrine organ, releasing a variety of peptides, cytokines, complement factors, and even components of the renin-angiotensin system into the circulation.[33] These substances collectively are referred to as adipokines. A report in which investigators studied the gene expression of cytokines obtained from subcutaneous fat in middle-aged obese women, specifically leptin, tumor necrosis factor-alpha

Table 38–3 Metabolic, Cardiovascular, and Renal Measurements

	Obese HTN (n = 55)	Lean HTN (n = 66)	Obese Norm (n = 21)	Lean Norm (n = 55)	P Value (ANOVA)
Total cholesterol (mg/dL)	225 ± 6	208 ± 6	203 ± 9	195 ± 4	0.009*
LDL cholesterol (mg/dL	153 ± 4	135 ± 6	131 ± 5	123 ± 7	0.048†, 0.037*
HDL cholesterol (mg/dL)	44 ± 2	54 ± 3	52 ± 3	59 ± 4	0.012†
Triglycerides (mg/dL)	182 ± 18	133 ± 10	120 ± 12	117 ± 12	0.037*
Insulin (μU/mL)	17.7 ± 1.3	11.1 ± 1.1	15.4 ± 2.2	10.9 ± 1.5	0.004†
LVM (g/m^2)	137 ± 7	135 ± 4	133 ± 4	120 ± 4	0.031*
SV/PP (mL/mm Hg)	2.17 ± 0.12	1.90 ± 0.08	2.26 ± 0.24	2.21 ± 0.13	0.042*
Creatinine clearance (mL/min)	121 ± 5	115 ± 4	127 ± 9	104 ± 4	0.005†
Urine sodium (mEq/day)	167 ± 13	159 ± 10	163 ± 16	153 ± 10	NS
AER (mg/day)	144 ± 16	101 ± 10	108 ± 13	85 ± 6	0.034†

* Hypertensive vs. normotensive, assessed by ANOVA.
† Lean vs. obese, assessed by ANOVA.
AER, albumin excretion rate; ANOVA, analysis of variance; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density

(TNF-α), IL-6, PAI-1, and adiponectin, provides an interesting insight into these factors.[34] In general, levels of leptin and adiponectin (which likely are protective substances) were lowest in women who had the greatest visceral fat volume. Fasting insulin concentrations correlated directly with adipose tissue TNF-α and IL-6 gene expression. Adiponectin gene expression was significantly lower in women with the metabolic syndrome than in those without it. These findings of a greater prominence of potentially harmful cytokines and a relative reduction of potentially protective factors like leptin and adiponectin help explain some of the adverse consequences of obesity.[34]

A study using the euglycemic hyperinsulinemic clamp in clinically healthy middle-aged men has further clarified these relationships.[35] Adiponectin concentrations correlated directly with glucose clearance rates, whereas TNF-α had a significant but inverse correlation with glucose clearance. In the same patients, total body fat (measured by dual energy x-ray absorptiometry) correlated inversely with adiponectin but directly with TNF-α. Thus, these two adipokines, adiponectin and TNF-α, have opposing effects on insulin resistance and have reverse relationships to body fat. This study also confirmed the relationship of CRP to TNF-α and obesity.[35]

The Renin-Angiotensin System

Adipose tissue expresses components of the renin-angiotensin system, especially angiotensinogen.[36,37] This effect is more pronounced in visceral than in subcutaneous fat.[36,37] If, indeed, this source of activity of the renin axis promotes meaningful systemic effects, it could help explain some of the renal and cardiovascular findings described earlier. It is by no means certain, however, that angiotensin mediates these changes to a marked extent in obesity. Our own findings have indicated, at least in hypertensive persons, that left ventricular muscle mass, for example, is more dependent on the renin-angiotensin system in lean persons than in the obese (for whom BMI was the only consistent predictor of LV muscle mass); and, as far as arterial stiffness is concerned, fasting plasma insulin, but not renin, is predictive of vascular properties in obese patients.[38] It is entirely possible, however, that regional expression of activity of the renin-angiotensin system—not measured in plasma—may play a role in mediating cardiovascular pathology in obesity.

The role of the renin-angiotensin system in insulin resistance and the genesis of diabetes may be particularly important. It is well established that blockers of the renin-angiotensin system including angiotensin receptor blockers and ACE inhibitors are effective in delaying or preventing new-onset diabetes in susceptible patients (see later). Mechanisms by which angiotensin II can promote insulin resistance and accelerate the appearance of diabetes include its effects on the microcirculation (particularly in skeletal muscle), insulin signaling within the pancreas, fibrotic changes in the islets and inhibitory actions—possibly including apoptosis—on β-cells (see reference 39 for review).

Other Factors Linking Obesity to Clinical Effects

The sympathetic nervous system has also been implicated as a mediator of the effects of obesity on cardiovascular and renal function.[36,40] Sympathetic hyperactivity, which can be stimulated by insulin resistance, is not uniform. In particular, renal sympathetic activity is enhanced in obesity[36,41] and may contribute to the sodium and volume retention that underlie the hypertension in such persons.

The role of leptin in the metabolic syndrome is not clear. Researchers know that it works in the hypothalamus, where it has appetite-suppressing activity and can influence sympathetic outflow. Levels of leptin are often increased in obesity, perhaps due to resistance to its effects. It has been speculated that obesity is associated with suppression of cytokine signaling proteins in the hypothalamus.[42] Interestingly, leptin has also been linked to findings such as increased left ventricular mass in obese patients,[43] although it is not clear whether this is a direct effect or is one mediated through such mechanisms as increased sympathetic drive that result from central effects of leptin.

An Additional Hypothesis

Generally, we have assumed that obesity is the main driver of insulin resistance and the metabolic syndrome, and there is little doubt that circulating adipokines released from fatty tissue play an important role in this. But it is also possible that intrinsic abnormalities within skeletal muscle cells and the liver could play a key role. There is compelling evidence from studies that use magnetic resonance spectroscopy that fatty acids are responsible for inhibiting insulin-stimulated glucose from being transported into skeletal muscle cells.[44] It appears that insulin resistance in humans results from defects in mitochondrial fatty acid oxidation in these cells. This causes accumulation of intracellular fatty acyl CoA and diacylglycerol, which, in turn, activate signal transduction pathways that inhibit insulin signaling.[45]

Underlying mitochondrial deficiency may have several causes including genetic abnormalities; aging; or, commonly, increased fat delivery due directly to high-caloric intake.[45] This mechanism could help explain why nonobese people can also develop insulin resistance and also why a reduction in caloric intake—even while previous obesity still exists—can provide immediate clinical improvement in the metabolic syndrome.

Finally, before considering the clinical details of the metabolic syndrome, it should be noted that obesity may have cardiovascular effects that are independent of the traditional risk factors associated with this syndrome. For instance, epidemiological evidence has suggested that increased body weight per se can increase the incidence of heart failure independently of other risk factors.[46] Indeed, a current report has described a linkage between impaired left ventricular diastolic function, as well as altered contractile reserve, with obesity and insulin resistance, again in subjects without any other features of the metabolic syndrome.[47] Further, all obvious risk factors associated with obesity can produce endothelial dysfunction, thus hastening adverse cardiovascular outcomes.[48]

Major Features of the Cardiovascular Metabolic Syndrome

Indicative of the protean features of this syndrome is that at times it has been given a variety of names: syndrome X,[49] the metabolic syndrome, the cardiovascular-metabolic syndrome,

Table 38–4 Clinical Findings Associated with the Cardiovascular Metabolic Syndrome

Metabolic
Central obesity
Hyperinsulinemia
High fasting glucose or impaired tolerance
Low HDL cholesterol
High triglycerides
Small, dense LDL cholesterol particles
Hyperuricemia
Cardiovascular
Hypertension
Endothelial dysfunction
Left ventricular hypertrophy or diastolic dysfunction
Increased arterial stiffness
Increased sympathetic activity
Renal
Microalbuminuria
Salt sensitivity
Hyperfiltration (high creatinine clearance)
Thrombotic
Increased fibrinogen levels
Increased plasminogen activator inhibitor-1
Inflammatory
Increased C-reactive protein, tumor necrosis factor, interleukin-6, and other inflammatory factors

and the hypertension syndrome.[50,51] None of these terms is entirely appropriate, for they do not include the renal, inflammatory, and thrombotic components of the full picture.

Major components of the syndrome are listed in Table 38–4. The manifestations of the syndrome can be divided roughly into five headings: metabolic, cardiovascular, renal, thrombotic, and inflammatory. Given the large number of items listed in Table 38–4 and bearing in mind that there are probably other associated findings that could be included, it becomes difficult and even arbitrary to propose a workable clinical definition of the syndrome. The current recommendations follow.

Current Definitions for the Syndrome

- Adult Treatment Panel III (ATP III): This recommendation, provided by the National Cholesterol Education Program (NCEP), bases the diagnosis on having any three of the following five clinical criteria:
  - Abdominal Obesity: waist measurement ≥40 inches (102 cm) in men or ≥35 inches (88 cm) in women
  - Hypertriglyceridemia: ≥150 mg/dL (1.7 mmol/L)
  - Low HDL Cholesterol: <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.
  - High Blood Pressure : ≥130/85 mm Hg
  - High Fasting Glucose Level: ≥100 mg/dL (5.5 mmol/L) (This was set originally at 110 mg/dL but was reduced to 100 mg/dL in recommendations of the American Diabetes Association.)
- World Health Organization (WHO): This definition of the metabolic syndrome requires fundamental evidence for insulin resistance (manifested by type 2 diabetes, impaired glucose tolerance, or high fasting glucose levels) together with two or more of the following abnormalities:
  - High Blood Pressure: ≥160/90 mm Hg
  - Hyperlipidemia: Triglycerides ≥150 mg/dL (1.7 mmol/L); or HDL cholesterol ≤35 mg/dL (0.9 mmol/L) in men and ≤39 mg/dL (1.0 mmol/L) in women
  - Central Obesity: Waist/hip ratio ≥0.90 in men or 0.85 in women; or a BMI ≥30 kg/m^2
  - Microalbuminuria: Urinary albumin excretion rate ≥20 mg/day or an albumin-to-creatinine ratio ≥20 mg/g

Broadly, the two definitions are similar in that they both depend on evidence for central obesity; insulin resistance (though, strictly speaking, the ATP III definition allows for a positive diagnosis if three of the findings are present, even in the presence of a normal fasting glucose level); lipid abnormalities; and high BP. Differences are interesting, however, with respect to BP. The WHO definition requires stage 2 hypertension, whereas the BP criterion for ATP III can be satisfied by a BP that is still in what is called the *prehypertensive range.* Also interesting is that the ATP III definition for obesity can only be satisfied by an increased waist circumference (reflecting the importance of visceral fat), whereas the WHO criterion can be satisfied, if the waist-hip criterion is not met, simply by a high BMI. WHO, but not ATP III, also accepts the presence of microalbuminuria as a criterion. There is little doubt that this particular finding is highly predictive of both cardiovascular and renal events. The choice of criteria and even the differences between the two definitions highlight the difficulty of completely defining this clinical picture; almost certainly these definitions will continue to evolve.

How Common Is the Metabolic Syndrome and What Are its Major Implications?

Approximately 24% of people in the United States have the metabolic syndrome.[52] The prevalence rates are similar for men and women except among African Americans, where women are 50% more likely than men to have the syndrome, and among people of Mexican origin, who are about 25% more likely than other ethnic groups to have the syndrome. Advancing age, at least from the 20s to the 60s, also appears to be linked to an increase in prevalence.

Among high-risk subpopulations, the metabolic syndrome is particularly common. For example, among people with diagnosed coronary heart disease, the prevalence of the metabolic syndrome (as defined by the ATP III criteria) was reported to be approximately 50%. Not surprisingly, coronary patients with evidence for the syndrome are more likely to have severe disease and a poorer prognosis than those who do not have it.[53]

In general, the metabolic syndrome predicts serious health consequences. A longitudinal follow-up of middle-aged men, without cardiovascular or other major disease at the onset of the study, found that those with evidence for metabolic syndrome were three times as likely to have a fatal event of any cause than those who did not have the syndrome.[54] In a similar observational study, not only mortality but also the

incidence of stroke and cardiovascular events was shown to be sharply increased by the presence of the metabolic syndrome.[55]

Antecedents of the Cardiovascular Metabolic Syndrome

On the basis of the previous discussion, it is easy to make the argument that obesity is the primary cause of metabolic syndrome. But just as not all obese people manifest the metabolic syndrome, it is also possible to develop the syndrome without being clinically obese. In fact, both the ATP III and WHO guidelines can be satisfied by criteria other than enlargement of waist circumference or increased BMI.

Although it has been persuasively argued that insulin resistance is a major mediator of the cardiovascular metabolic syndrome,[56] the possibility of a genetic predisposition has been raised by a familial pattern noted in some patients. Certainly, in the context of what has been called the *hypertension syndrome*—which, in essence, is a common form of the metabolic syndrome that includes unequivocally raised BP—there is evidence that cardiovascular and renal changes can appear at an early stage of life.

Familial Trends

It is difficult to ascribe specific causes for clinical findings that appear in successive generations of a family. A genetic basis could very well exist, but at the same time, because family members often adopt similar eating and lifestyle habits, the resemblance could simply reflect a commonality of the living environment. Still, abnormal findings in the relatively young normotensive offspring of hypertensive parents suggest that there may be antecedents for the metabolic syndrome in some individuals that are independent of later obesity.

In a cohort of young adults identified by screening, those with normal BPs who had a positive family history of hypertension (either through one or both parents or siblings) were matched by age and body weight with young adults who did not have such a family history.[50,51] By comparison with the group without a family history, those with a positive history had significantly higher values for LDL cholesterol, triglycerides, and insulin levels. Plasma renin activity and norepinephrine measurements also tended to be higher. Moreover, left ventricular muscle mass was greater, and there was a lower E/A ratio on echo-Doppler measurement,[57] indicating a greater dependency of diastolic filling on late atrial contraction, perhaps due to early left ventricular stiffening. Arterial compliance, particularly that measured in the microcirculation, was also lower (indicating greater arterial stiffness) in those with a positive family history.[58]

Evidence indicates that a positive family history of hypertension is predictive of increased creatinine clearance (hyperfiltration) in normotensive offspring.[50] Normotensive children of hypertensive parents have also been shown to have increased sympathetic activity.[59] These findings appear to be independent of obesity, although it has been separately reported that obese children (in their early teens) are more likely than normal-weight children to have microalbuminuria.[60] These findings support the claim that genetic factors—and not just acquired obesity—could play an important role in the genesis of the cardiovascular metabolic syndrome.[61]

The Issue of Hypertension

Earlier on, in discussing the "hypertension syndrome," it was pointed out that some of the mediators of the cardiovascular and renal aspects of this form of the cardiovascular metabolic syndrome appeared to differ between obese and lean hypertensives. In obese individuals, body weight and insulin levels appeared to be most predictive of clinical abnormalities, whereas in lean patients there appeared to be a greater participation of the renin-angiotensin and sympathetic systems. In addition, lipid and insulin levels (as summarized in Table 38–3) differed between the obese and lean hypertension groups.[26]

Other important differences between obese and lean hypertensives exist. The fundamental hemodynamics of the two forms of hypertension depend on separate mechanisms: In obese hypertensives, presumably reflecting their tendency to sodium and volume retention, the hypertension is characterized principally by an increase in stroke volume (cardiac output) but with a normal peripheral resistance; in lean hypertensives, perhaps reflecting their dependency on heightened neurohumoral activity, cardiac output is normal but peripheral resistance is increased.[62-64]

Perhaps the most meaningful difference between obese and lean hypertensives is the apparently paradoxical finding that obese hypertensive patients actually have a better long-term prognosis regarding cardiovascular mortality and morbidity.[65,66] Interestingly, this finding does not apply only to people with hypertension: Similar findings have been shown for patients with established coronary disease, among whom—somewhat in contradiction to some epidemiologic reports (see earlier)—the lean patients appear to have a poorer prognosis.[67] In the hypertension setting, obese patients have an apparent advantage even when all other risk factors are taken into account.[66] It should be emphasized, however, that even though obese hypertensive patients appear to have better outcomes than lean hypertensives, they still have a poorer prognosis than normotensive controls.[65,66]

Explanations for these disparate outcomes are not immediately obvious. Even though lean patients may be more dependent on renin and sympathetic mechanisms for some of their cardiovascular and renal lesions, a detailed review of studies in which such neuroendocrine measurements were provided showed no consistent trends indicating that these systems were activated in either type of hypertension.[68] Our own observations indicated that plasma renin activity and catecholamine measurements were similar in obese and lean hypertensive patients and similar to such measurements in obese and lean controls with normal BP.[26]

A more promising line of inquiry has focused, not on the resting values of the systems, but on their reactivity to stress. As shown in Figure 38–2, during standardized treadmill testing, there were significantly greater increases in plasma renin activity in lean hypertensives than in obese hypertensives; likewise, there were significantly greater increases in plasma epinephrine in the lean than in the obese groups. Particularly noteworthy is that findings in the normotensive obese and lean patients are virtually identical to those in the corresponding hypertensive groups (see Fig. 38–2). If we make the reasonable assumption that the findings in lean people with normal BP represent the appropriate physiologic response to stress testing, then it can be concluded that obese

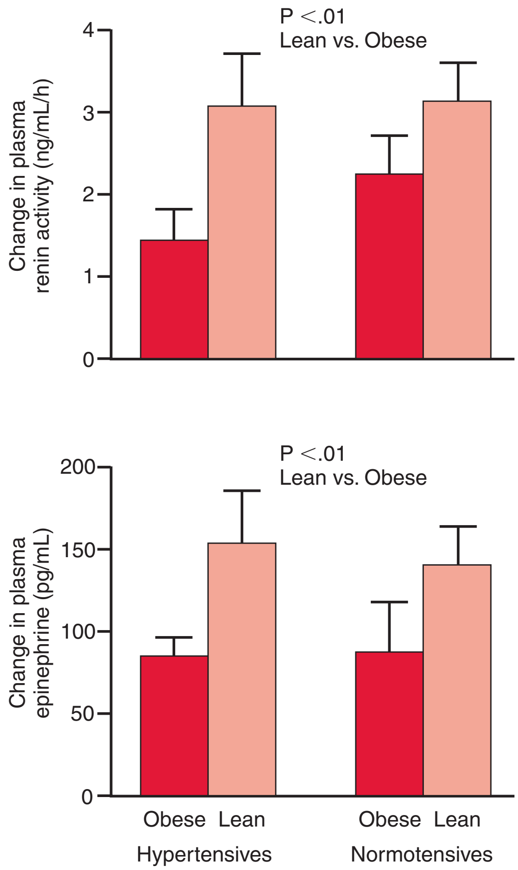

Figure 38–2 Changes in plasma renin activity and in plasma epinephrine concentrations during treadmill testing in obese and lean hypertensive patients and normotensive volunteers. By two-way ANOVA, the differences between the obese and lean subjects were significant, but not the differences between hypertensives and normotensives. (From Melnik TA, Rhoades SJ, Wales KR, et al: Overweight school children in New York City: Prevalence estimates and characteristics. Int J Obes Relat Metab Disord 1998:22: 7-13.)

individuals—either hypertensive or normotensive—exhibit an inhibited neuroendocrine response to this type of stimulation.[26] This finding could either explain a possible protective mechanism in obese hypertensive individuals or the unexpectedly poorer outcomes in lean hypertensive patients. Other data also support the concept of greater neuroendocrine reactivity in lean hypertensive patients.[69] Taken together with the full array of clinical differences between the two hypertensive groups, it can be hypothesized that they represent two distinct clinical entities.

Even though we have no direct mechanistic evidence that volume-dependent hypertension may be more benign than vasoconstrictor-dependent hypertension, there is one clear clinical consequence. An interesting subgroup analysis derived from the Systolic Hypertension in the Elderly Program (SHEP) demonstrated that the diuretic agent chlorthalidone was particularly effective in improving cardiovascular disease outcomes in overweight and obese elderly hypertensive patients but actually appeared to worsen morbidity and mortality in lean patients.[70] More studies of this type would be helpful in further characterizing optimal therapeutic approaches to these different types of hypertension. Studies of genetic characteristics would also be of interest: Do patients with obese and lean hypertension have two separate genetic forms of hypertension? Or, in the particular case of obese people, can hypertension be attributed partly or even entirely to environmental factors?

PREVENTION AND TREATMENT OF OBESITY AND THE METABOLIC SYNDROME

Lay people, as well as health professionals, obviously know that the primary therapeutic approach to obesity is a reduction in energy consumption and an increase in physical activity. In a society that is highly conscious of personal appearance, few, if any, obese people are not aware of their condition and have not made numerous attempts to deal with it. But this problem, which, in the minds of those fortunate enough to be lean, reflects the self-indulgence or lack of willpower of their heavier contemporaries, is obviously more complex.

An innovative study has compared activity levels during the routine daily lives of mildly obese and lean volunteers.[71] Body sensors were used to carefully measure changes in posture and movement (called *nonexercise activity thermogenesis*) on a continuous basis during 10 days of observation. It was found that obese people were seated for 2 hours longer each day than their lean counterparts. Interestingly, when as part of the study the obese people lost weight and the lean people gained weight—thus largely eliminating the weight differential between the groups—their patterns of activity still remained constant. The investigators concluded that this type of activity appears to be biologically determined rather than governed by body weight, and so creates the possibility that genetic differences may play an important role in the development of obesity. The lean group expended about 350 calories a day more than the obese group due to their heightened daily movements. This could potentially be of great importance because this type of activity, which generally cannot be measured in the standard clinical setting, could account for a difference of as much as 30 lb in body weight during the course of a year. Thus, our traditional assumptions about diet and exercise may be oversimplifying the issue of obesity.

Practical Approaches

Strategies for dealing with this problem can broadly be divided into three groups. First are those strategies targeted at preventing or reversing obesity. Then, there are those targeted at people who already have evidence for the metabolic syndrome, which are focused both on preventing or reversing obesity and on preventing progression of insulin resistance into clinical type 2 diabetes. Finally, in addition to the first two strategies, there are treatments aimed at the risk factors associated with the metabolic syndrome and at protecting against cardiovascular and renal events.

The obesity problem has no simple solutions. Public policy remains a cornerstone of preventing and dealing with this issue. Certainly, the traditional health care setting can only be a small part of such a campaign. There must be a strong focus

in schools and other places of education including colleges. Starting this education at a young age is clearly important, and even nursery and kindergarten facilities, as well as after-school and day-care facilities, must focus on teaching good eating habits to young children and providing them with appropriate diets.[6,7] Educating parents, as well as children, about good food choices is essential, as is providing proper exercise facilities. Churches and other places of worship, work sites, and clubs are other places in the community where this pervasive problem can be addressed.

The American College of Physicians has published guidelines for the management of obesity.[72] As shown in Figure 38–3, the recommended algorithm depends chiefly on weight loss, diet, exercise, and other appropriate lifestyle changes. Drug therapy is regarded as an adjunct to a structured lifestyle regimen that is tailored to individual patients.

Uncertainty exists regarding the optimal diets to be recommended for the management of obesity. Traditionally, we have employed low-fat diets and have attempted to reduce caloric intake as much as possible. This approach, given enough time, can undoubtedly effectively reduce body weight, particularly if accompanied by an appropriate aerobic exercise regimen. Apart from contributing to weight loss, exercise also has a beneficial effect on insulin sensitivity, although it has inconsistent effects on inflammatory biomarkers, as measured by levels of C-reactive protein and adiponectin.[73]

There is great current interest in the use of very low carbohydrate diets (sometimes referred to as *ketogenic diets*). This approach has been popular with the lay public because not only are results, in terms of reduced body weight, relatively prompt, but there is no compelling need to practice denial in terms of the quantities of food consumed. Strictly speaking, as long as carbohydrates are avoided, there are no real limitations on other types of foods. There is no evidence that this approach will adequately reverse the cardiovascular metabolic syndrome; beyond that, there is no real evidence regarding the effects of these diets on long-term cardiovascular prognosis. A report of the short-term effects of a low-carbohydrate diet, which interestingly resulted in a meaningful reduction in calorie intake, has demonstrated significant improvement in glucose and insulin metabolism and lipid levels.[74] A thoughtful review of these issues, together with the possible benefits of differing exercise strategies, has been published.[75]

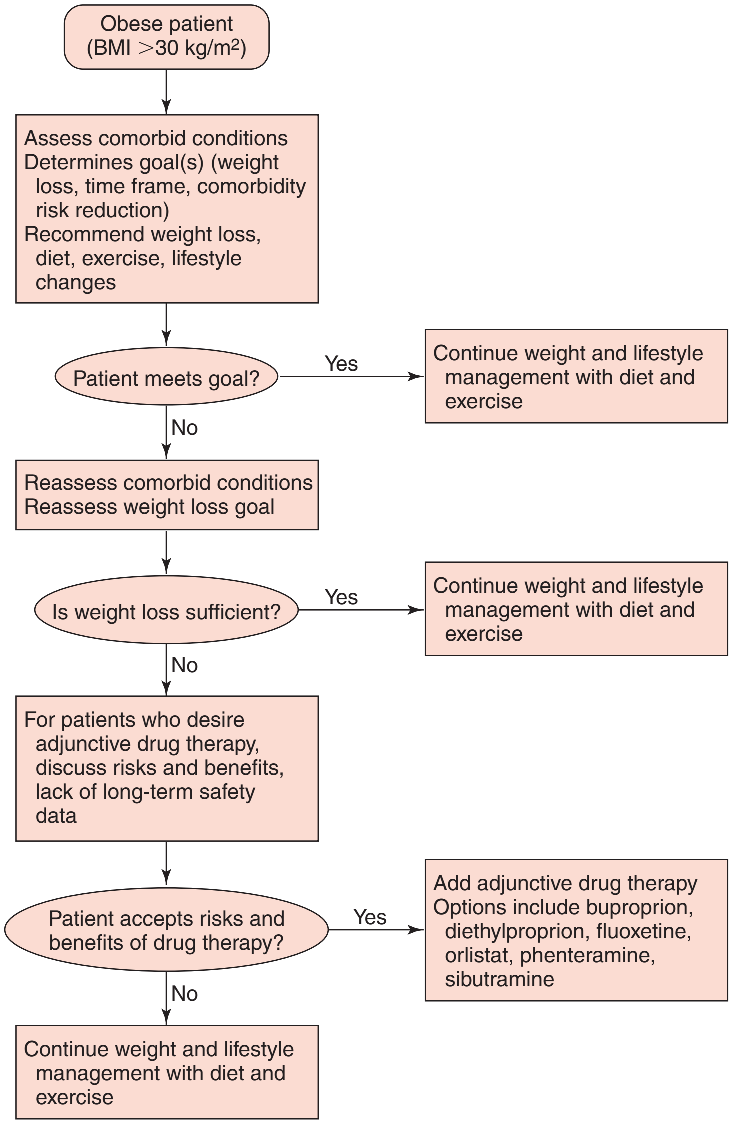

Figure 38–3 Algorithm for managing obesity in clinical practice. This clinical practice guideline was sponsored by the American College of Physicians. (From Snow V, Barry P, Fitterman N, et al: Pharmacologic and surgical management of obesity in primary care: A clinical practice guideline from the American College of Physicians. Ann Intern Med 2005;142:525-31.)

Drug Therapy

The two main agents that are currently prescribed are sibutramine, a serotonin and norepinephrine reuptake inhibitor, and orlistat, an inhibitor of pancreatic lipase. Sibutramine produces decreased appetite and early satiety.[76] This drug is effective in producing weight loss for as long as it is actively taken. The main safety concerns are the increases in BP and pulse rate that occur in some patients; for individuals with more severe forms of hypertension, the use of this agent may be questionable. A meta-analysis of trials using sibutramine in overweight or obese patients has demonstrated a mean weight loss of 4.5 kg compared with placebo after 12 months.[77]

The main effect of orlistat is to impair digestion of about one third of the fat in the diet. Because this results in a reduction in absorption of dietary fat, there is a reduction in caloric intake. At least one study has claimed that, together with appropriate nonpharmacologic therapy, this agent can reduce the incidence of new-onset diabetes in obese people.[78] Because this drug works by inducing a form of malabsorption, not surprisingly most of its symptomatic side effects are linked to steatorrhea. A meta-analysis of clinical trials with orlistat in obese patients showed a mean weight loss of 2.9 kg after 12 months of treatment.[79]

The two other drugs approved by the Food and Drug Administration for appetite suppression are phentermine and diethylpropion. They are both sympathomimetic amines, with side effects of tachycardia and palpitations, as well as gastrointestinal symptoms. A meta-analysis[80] revealed modest efficacy: for phentermine, there was a mean weight loss of 3.6 kg and for diethylpropion, 3.0 kg. Some evidence indicates that selective serotonin re-uptake inhibitor-type antidepressants like fluoxetine and sertraline can have appetite-suppressant effects.

Rimonabant is a new compound that works in the central nervous system as an antagonist of the cannabinoid-1 receptor. Apart from its efficacy in inducing meaningful weight loss, this agent has also undergone successful clinical trials for cessation of smoking and alcohol use. There is also reason to believe that this agent, apart from inducing weight loss, improves the lipid profile.[81] Experience with rimonabant is still relatively limited because it has not yet been registered for general use, but early indications are that it is well tolerated. If this proves to be the case, it may become a valuable tool for managing obese patients who, despite efforts to adopt lifestyle changes, remain at unacceptably high body weights.

Surgical Therapy

In addition to drug therapy, surgical procedures are also now being commonly undertaken for severely obese patients including adolescents who have been unsuccessful in losing weight by other means. Because some of these surgeries can be performed laparoscopically, they are becoming progressively more popular, though they are certainly not free of complications. Procedures such as vertical banded gastroplasty or gastric bypass are unquestionably efficacious in assisting weight loss. It has also been reported that, together with their substantial weight loss, these patients experience significant improvements in components of the metabolic syndrome including systolic blood pressure, total cholesterol, triglycerides, and glucose.[82] Moreover, the benefits of surgical procedures appear to persist over long time periods. A 10-year follow-up of Swedish patients has shown that meaningful weight loss was maintained throughout this period and was associated with a reduced incidence of diabetes and hypertension when compared with patients not having surgery.[83]

Prevention

On a positive note, data from diabetes prevention studies indicate that even moderate lifestyle interventions by diet and exercise in people with impaired glucose tolerance and other aspects of the metabolic syndrome can decrease significantly the incidence of type 2 diabetes.[84] In particular, the Diabetes Prevention Program demonstrated that a weight loss of at least 5% together with at least 2 to 2 1/2 hours of structured physical activity a week produced a better than 50% reduction in new-onset diabetes compared with undertaking no lifestyle modification. The use of the antidiabetes drug metformin was about half as effective in preventing incident diabetes as lifestyle modification alone.[85] Figure 38–4 summarizes the main findings of this important 4-year trial.

Preventing Diabetes

In addition to weight-loss strategies, other important aspects of the cardiovascular metabolic syndrome can also be addressed. A primary objective in managing these patients is to prevent progression of the metabolic syndrome into the full clinical picture of type 2 diabetes. The best success so far has been with blockers of the renin-angiotensin system. For example, in the Heart Outcomes Prevention Evaluation (HOPE) study, carried out in patients at high risk of cardiovascular events, many of whom had characteristics of the metabolic syndrome, an ACE inhibitor reduced new-onset diabetes by 30% when compared with placebo.[86] Of particular note, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), it was reported that in patients with impaired fasting glucose levels at baseline

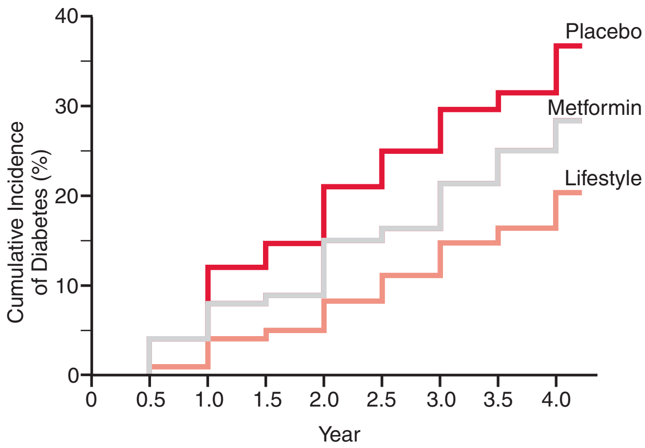

Figure 38–4 New-onset diabetes during 4 years of observation. The rates in the three arms are significantly different from each other ($P < 0.001$). (From Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.)

(110 to 125 mg/dL), the use of diuretic-based therapy was associated with a greater than 50% conversion to frank diabetes by the end of the 4-year study. This conversion was significantly lower with an ACE inhibitor than with a diuretic, though still troublingly high (36%) in these very susceptible patients.[87]

In high-risk hypertensive patients in the LIFE study, the angiotensin receptor blocker losartan reduced new-onset diabetes by 25% when compared with the β-blocker atenolol.[88] In the VALUE trial, also carried out in high-risk hypertensive patients, valsartan was 23% more effective than amlodipine in preventing diabetes. This was a meaningful finding because calcium channel blockers—unlike diuretics or β-blockers—may have some slightly beneficial effects on glucose metabolism, thus making the finding with valsartan particularly important.[89]

The oral anti-diabetic agent metformin has also been shown to be effective in preventing diabetes.[85] Also of great interest are the peroxisomal proliferator-activated receptor (PPAR) drugs, which affect the nuclear transcriptional regulators that govern insulin resistance as well as lipid profiles and probably other factors influencing the genesis of vascular disease. Cardiac function may also be improved: A trial with pioglitazone in hypertensive patients demonstrated an enhancement of left ventricular diastolic function that was most evident in those whose measures of insulin sensitivity were improved, most likely reflecting increases in adiponectin and matrix metalloproteinase (MMP-2) produced by this agent.[90] Clinical trials are now examining whether the PPAR agents, generally referred to as thiazolidinediones, already known to be effective in treating type 2 diabetes, can also be shown to prevent or delay diabetes.[91] Similarly, a major clinical trial with the antidiabetes agent nateglinide is currently under way in susceptible patients to measure its potential ability to prevent or delay type 2 diabetes.[92]

Other Approaches

From the viewpoint of the practicing clinician, the goal of managing patients with obesity and its associated abnormalities is to protect them from cardiovascular events. Rigorous control of hypertension and lipid abnormalities are cornerstones of therapy. Blockers of the renin-angiotensin system have much to offer because, in addition to diminishing the rate of new-onset diabetes, they reduce microalbuminuria and prevent its progression to diabetic nephropathy.[93] Further, in patients already manifesting nephropathy, they can significantly reduce progression to end-stage renal disease.[94,95] Moreover, preliminary evidence suggests that angiotensin receptor blockers reduce the cytokines and inflammatory agents that may mediate cardiovascular disease in obese patients. For instance, olmesartan was shown to reduce CRP, TNF, and interleukin-6 during 3 months of treatment in high-risk hypertensive patients.[96]

Some angiotensin receptor blockers appear to have relevant effects, independent of their blockade of angiotensin II, that rely on their partial PPAR-γ against actions. In vitro studies have demonstrated that both telmisartan and irbesartan stimulate adiponectin expression, and studies in an obese rat model showed attenuation of adiponectin depletion together with improved insulin sensitivity when irbesartan was administered.[97]

The clinical and research communities now recognize obesity and the cardiovascular metabolic syndrome as precursors of diabetes and major cardiovascular and renal events. Our growing use of the modern drugs already discussed, along with new types of PPAR agents, more powerful statins, and antiplatelet therapies, which, together with effective antihypertensive therapy could reduce the clinical consequences that arise from the metabolic syndrome, indicates a broad awareness of these problems. These innovative therapies have potential for complementing the results of effective lifestyle strategies.

A Final Caveat

Despite the wide acceptance of the metabolic syndrome as an important clinical entity, some significant observers have raised a cautionary note. A joint statement of the American Diabetes Association and the European Association for the Study of Diabetes points out that while some key cardiovascular risk factors tend to cluster together, and perhaps are linked to obesity and insulin resistance in many cases, the term "syndrome" is not fully justified.[98] They note that the definition of the syndrome is arbitrary and includes people with a potentially wide range of clinical phenotypes that could reflect differing pathophysiologic mechanisms. These experts recommend dealing with all cardiovascular risk factors in an appropriate fashion, regardless of whether or not individuals meet the current criteria for diagnosing the metabolic syndrome. From a pragmatic point of view, this advice confirms what responsible clinicians are already doing.

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Chapter 39

Hypertension in Pregnancy

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CHAPTER CONTENTS

Hypertension is the most common medical complication of pregnancy, affecting 10% to 15% of all pregnancies in the developed world. It is the second leading cause of maternal death and increases the incidence of preterm birth, intrauterine growth restriction, placental abruption, and perinatal mortality. Hypertension in pregnancy may be due to underlying chronic essential or secondary hypertension, gestational hypertension, or preeclampsia; the latter two disorders are unique to human pregnancy. Importantly, each of these etiologies has a distinct hemodynamic profile, apparent mechanism, risk to mother and fetus, and long-term sequelae. Differential diagnosis of hypertension during pregnancy can be surprisingly difficult. Furthermore, normal physiological adaptations to pregnancy often mask evidence of underlying (preconceptual) hypertension.

Although clinical trial and outcomes data guide treatment goals or blood pressure (BP) targets in nonpregnant hypertensive patients, we are without evidence-based BP targets for hypertensive gravidas. Defining BP targets is even more difficult because guidelines were developed using mercury sphygmomanometry, while practice has largely shifted to use of automated oscillometric BP devices, despite their often erroneous results in hypertensive pregnant women. Tight BP control appears not to benefit women without target organ damage. However, the risk of cerebrovascular catastrophe when BP exceeds either 170 systolic or 110 diastolic should focus our efforts both on avoiding these high levels and on early recognition of preeclampsia, which may evolve rapidly and unpredictably toward multisystem failure and life-threatening complications. Antihypertensive therapy is limited by contraindications to the use of angiotensin-converting enzyme (ACE) inhibitors and AT_1 receptor blockers late in pregnancy and by a paucity of well-designed and adequately powered studies to assess risks and benefits of other antihypertensive agents. This lack of data has not stemmed the profusion of meta-analyses and consensus treatment guidelines.

BLOOD PRESSURE MEASUREMENT AND NORMS DURING PREGNANCY

Hypertension in pregnancy is defined as a BP >140 mm Hg systolic or > 90 mm Hg diastolic, occurring at any time during pregnancy.[1] BP measurement during pregnancy is best performed in the sitting position, with the arm supported, using an appropriately sized cuff, a mercury sphygmomanometer, and defining diastolic BP as the fifth Korotkoff sound.[2] Supine BP may be elevated late in pregnancy in some women due to mass effect of the gravid uterus. This has led many clinicians erroneously to favor BP measurement in the left lateral decubitus position. When BP is then recorded from the right arm (inadvertently elevated relative to the heart), it can be falsely reassuring. By contrast, when it is impractical for the patient to sit for BP measurement, a reasonable and conservative strategy would be to record BP from the left (inferior) arm. Most of the oscillometric devices now used routinely for BP measurement in hospital clinics, on labor and delivery units, and even those that are integral to fetal monitoring devices have not been validated in hypertensive pregnant women; nearly all provide erroneous calculations of diastolic BP. Because many guidelines for treatment of severe hypertension focus on diastolic values, all automated readings should be confirmed by auscultation when they might affect therapy.

Even though oscillometric devices may be inaccurate in hypertensive gravidas, home BP monitoring by women at high risk for preeclampsia or with more severe underlying hypertension can be extraordinarily useful by detecting significant changes in systolic pressure, leading to early diagnosis of preeclampsia or to more careful titration of antihypertensive medications.[3] Similarly, there may be promise in the use of ambulatory BP monitoring for risk assessment in pregnancy, though confirmatory and outcomes data remain lacking.[4]

RISKS OF HYPERTENSION IN PREGNANCY AND GUIDELINES FOR EVALUATION AND MANAGEMENT

Chronic hypertension increases risks of several morbid pregnancy outcomes including superimposed preeclampsia, preterm birth, intrauterine growth restriction, placental abruption, perinatal death, and accelerated hypertension threatening the mother.[5-7] Antihypertensive treatment fails to prevent these outcomes, except for the occurrence of more severe hypertension later in pregnancy. This remains important because adverse perinatal outcomes seem closely related to severity of maternal hypertension and because severe hypertension may be a major cause of both hospitalization and early delivery. Recognition of these risks and of clinical uncertainty regarding evaluation and treatment of hypertensive gravidas has led to updated guidelines by consensus groups in the United States, Canada, and Australia.[2,8,9]

All of the consensus groups agree, even without clear outcomes data, that BPs as low as 170/110 mm Hg can lead to cerebrovascular hemorrhage during pregnancy, making treatment of such pressures a medical emergency. At the opposite extreme, it has been suggested, but not proven, that tight BP control may impair fetal growth.[10] The Australasian Society for the Study of Hypertension in Pregnancy suggests maintaining BPs < 140/90 mm Hg.[8] The Canadian Hypertension Society suggests similarly tight control only for some groups of women.[9] By contrast, the National High Blood Pressure Education Program (NHBPEP) Working Group on Hypertension in Pregnancy suggests (re)instituting drug therapy at pressures of 150 to 160/100 to 110, targeting lower pressures in selected patients with target organ damage or underlying renal disease.[2] Not only is there disagreement among national groups, but disagreement occurs even within one system: a survey of Canadian practitioners with experience in the care of hypertensive pregnant women revealed no consensus regarding appropriate BP targets.[11] These uncertainties should provide the equipoise and impetus for adequately powered prospective trials to guide therapy instead of continued appeal to well-meaning guidelines.

HEMODYNAMICS IN NORMAL AND HYPERTENSIVE PREGNANCY

Normal pregnancy leads to significant hemodynamic and renal adaptations that affect our approach to hypertension. Gestational systemic vasodilation is so prominent that, despite an increase in cardiac output (CO) of nearly 50%, BP falls early in the first trimester.[12,13] Paradoxically, this gestational hypotension is even more prominent in women with underlying chronic hypertension, so BP may fall by 30/15 mm Hg, masking the recognition of pregestational hypertension when the patient is examined at her first prenatal visit.[14] Thus a thorough history, review of records, funduscopic examination, and evidence of target organ damage may be the only good clues to chronic hypertension in the early phase of pregnancy; BP values of 120/80 during the first trimester may be abnormal and should lead to suspicion of underlying hypertension. The mechanisms of gestational vasodilation remain uncertain but appear not to depend on either vasodilator prostaglandins or nitric oxide (NO).

Pregnancy leads to major changes in the renin-angiotensin-aldosterone system, with markedly increased levels of angiotensinogen, plasma renin activity, angiotensin II, Ang 1-7, and aldosterone.[15,16] However, there is a specific refractoriness to the vascular AT_1 receptor-mediated effects of angiotensin, manifest as decreased pressor response to infused angiotensin II and to blunted constriction of human resistance arteries in vitro.

Pregnancy leads to generalized systemic vasodilation, and specifically to renal vasodilation and hyperfiltration, with balanced afferent and efferent arteriolar vasodilation and parallel increments of renal plasma flow and glomerular filtration rate (GFR).[13] In the same way that pregnancy may obscure the recognition of underlying essential hypertension, this gestational hyperfiltration may mask underlying renal insufficiency (chronic kidney disease, CKD). A serum creatinine concentration of > 0.8 mg/dL early in pregnancy should be viewed with suspicion. The mechanisms leading to gestational renal vasodilation have been elucidated in the rat and appear to depend on a cascade in which the ovarian hormone relaxin acts via gelatinase to cleave big endothelin (ET), resulting in ET_B receptor-mediated activation of NO synthase.[17] Whether similar mechanisms occur in women is yet to be determined.

DIAGNOSIS AND CLASSIFICATION OF HYPERTENSION IN PREGNANCY

We now recognize four diagnostic categories for hypertensive disorders of pregnancy, using a nomenclature endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP), several national and international obstetrics groups, and by the NHBPEP Working Group on Hypertension in Pregnancy.[1,2] Chronic hypertension (antedating pregnancy) may be either essential or secondary. Two hypertensive disorders occur only in pregnancy: gestational hypertension and preeclampsia. Finally, preeclampsia may be superimposed on underlying chronic hypertension. Obsolete terms, such as pregnancy-induced hypertension (PIH), usually include a mix of disorders, with differing pathophysiology and risks. The literature, ongoing research, and our patients are ill served by their continued use.

Chronic Hypertension

With postponement of childbearing to more advanced age and the epidemic of essential hypertension, often coupled with obesity and insulin-resistance, this is the most rapidly growing cause of hypertension in pregnancy. Though less common than essential hypertension, three forms of secondary hypertension that affect young women are worth specific mention: pheochromocytoma, renovascular hypertension, and primary hyperaldosteronism.[14] Despite its rarity, physicians should have a low threshold for suspecting pheochromocytoma when hypertension is associated with classic symptoms and signs because it may lead to hypertensive crisis during labor. Suspicion of pheochromocytoma should lead to α-adrenoreceptor blockade and confirmatory measurements of catecholamines and their metabolites. Several cases of life-saving surgical management with proper pharmacologic blockade of pheochromocytoma during pregnancy have been

reported.[18] Renovascular hypertension, most likely due to fibromuscular dysplasia or arteritis in women of childbearing age, carries such a high risk of superimposed preeclampsia and poor outcome that it should be corrected before or even during pregnancy if diagnosed. Diagnosis is difficult because usual measurements of circulating elements of the renin-angiotensin system are of little to no diagnostic utility during pregnancy; Doppler ultrasound measurements are often misleading, and radionuclide renal scans are avoided in pregnancy. Further, radiology colleagues often hesitate to perform MRI or interventional procedures, even when indicated. Notwithstanding these obstacles, there are case reports of diagnosis by magnetic resonance angiography and of correction by angioplasty during pregnancy with good outcome.[19] Finally, hypertension due to primary hyperaldosteronism may have a variable and often surprisingly benign course during pregnancy because high levels of progesterone during pregnancy can antagonize mineralocorticoid effects at the aldosterone receptor.[15,20] In these cases, severe hypertension and hypokalemia may be unmasked postpartum.

Importantly, many apparently healthy young women have never had BP measurement or routine medical care. This then conspires with normal gestational vasodilation and relative hypotension to obscure the diagnosis of underlying chronic hypertension, which may then only be recognized later in pregnancy and mistaken for either gestational hypertension or preeclampsia.

Gestational Hypertension

Gestational hypertension is hypertension occurring de novo, usually during the latter half of pregnancy in the absence of proteinuria and other signs or symptoms of preeclampsia and resolving postpartum. Although it may result in severe hypertension requiring treatment, its course is usually more benign than that of preeclampsia. It may recur in subsequent pregnancies and often predicts essential hypertension or, like preeclampsia, increased cardiovascular risk later in life.

Preeclampsia

Preeclampsia is characterized by de novo hypertension, usually during the latter half of pregnancy, though well-characterized cases have been reported as early as 16 weeks. However, it is a multisystem disorder, usually defined by proteinuria (> 300 mg/day) and resolving postpartum. It occurs in approximately 6% of (usually primigravid) pregnancies. Risk factors, listed in Table 39–1, include a family history of preeclampsia, multifetal gestation, diabetes mellitus, renal or autoimmune diseases, and obesity with insulin resistance. In addition, a variety of unrelated genetic abnormalities including mutations of angiotensinogen or nitric oxide synthase genes seem to increase the risk of preeclampsia in some populations. Whereas clinically evident target organ damage characterizes more severe disease, subtle symptoms or laboratory evidence of target organ damage including hyperuricemia, thrombocytopenia, and abnormalities of liver function or coagulation tests are common. Because preeclampsia can have a variable course and explosive clinical evolution,[21] with real risks of maternal morbidity and mortality, one should err toward diagnosing preeclampsia, even in the absence of proteinuria (which can occur later in the evolution of the disorder), when hypertension is accompanied by abdominal pain, neurological symptoms, such as headache or blurred vision, or any evidence of thrombocytopenia or liver function or coagulation abnormalities.[2] Preeclampsia can evolve rapidly to a convulsive and life-threatening phase termed eclampsia. An especially threatening variant of preeclampsia is the HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome, which may seem mild in its initial presentation, then evolve over hours to microangiopathic hemolysis, severe thrombocytopenia, and hepatic necrosis with rupture.

Distinguishing preeclampsia from gestational hypertension by the detection of proteinuria and by hemodynamic assessment may be difficult. Obstetricians in the United States typically screen for proteinuria using urine dipsticks, confirming positive (1+) results by 24-hour urine collection (using unspecified methods for quantitation of 24-hour urine protein and a cutoff value of 300 mg). This "gold standard" case definition is based on historical studies of clearly defined cases, before the availability of sensitive and specific methods for assessment of albuminuria or excretion of other specific urine proteins. Many gravidas with proteinuria exceeding this threshold will prove to have no glomerular protein leak; 500 mg/day proteinuria, or some new definition of pathological albuminuria, may better predict morbid maternal and fetal outcomes.[22] Further, the sensitivity of urine dipsticks and their prediction of 24-hour urine protein are poor, due in large part to variations in urine concentration. This limitation may be overcome by efforts to standardize screening techniques on the basis of measurement of albumin-to-creatinine ratios, correction for urine specific gravity, or use of automated point-of-care devices.[23,24] Although proteinuria may occur in synchrony with hypertension in proteinuria, it may be delayed, in some cases by many weeks.[25] This explains why the diagnosis of preeclampsia can only be made with any certainty in retrospect and may also explain the common misconception that gestational hypertension may evolve into preeclampsia. In the future, markers such as sFlt-1 or AT_1 receptor autoantibodies (see later) or convenient, noninvasive hemodynamic measurements may likely allow for a more certain differential diagnosis during pregnancy. We await adequately powered prospective studies that link these

Table 39–1 Risk Factors for Preeclampsia

Primigravida
First pregnancy with this partner
Family history of preeclampsia
Multifetal pregnancy
Preeclampsia in prior pregnancy
IUGR, placental abruption, or fetal demise in prior pregnancy
Obesity
Renal disease of any cause or severity (including microhematuria or microproteinuria without specific etiological diagnosis)
Diabetes mellitus
Chronic hypertension
Connective tissue disease

IUGR, intrauterine growth restriction.

markers to outcomes in women at normal and elevated risk for preeclampsia or superimposed preeclampsia.[26]

Superimposed Preeclampsia

"Pure" preeclampsia complicates approximately 6% of (usually primigravid) pregnancies. It can, in addition, be superimposed on 20% to 40% of pregnancies in women with underlying chronic hypertension or other predisposing medical diseases including even minor renal disease of any cause, such as early diabetic nephropathy, autoimmune disease, or even microscopical hematuria.[27,28] Superimposed preeclampsia is apt to be more severe, with greater risks to mother and fetus, than preeclampsia without predisposing medical disorders, and it is more apt to recur in subsequent pregnancies. Superimposed preeclampsia and progression to more severe hypertension represent the two major risks of chronic hypertension in pregnancy. Often it is difficult to decide when an already-hypertensive or already-proteinuric woman's course has worsened due to the onset of superimposed preeclampsia. Indeed, in a classic study using renal biopsies to verify diagnosis, a nephrologist and obstetrician correctly diagnosed preeclampsia and distinguished it from competing disorders in parous women in only 58% of cases.[29] Because we now believe that sFlt-1 accounts for the typical renal lesion of "glomerular endotheliosis,"[30] we might presume that a study assessing its diagnostic accuracy would demonstrate similar discordance in parous women or in those with underlying disease, though this remains to be determined. Proteinuria in women with pregestational glomerular disease will usually worsen during pregnancy, often to nephrotic levels. We advocate a strategy of close monitoring, repeatedly re-establishing baseline data in order to detect interval changes in BP, proteinuria or albuminuria, symptoms, or blood test results, which might suggest superimposed preeclampsia.

PATHOPHYSIOLOGY OF PREECLAMPSIA AND ECLAMPSIA

Elegant invasive hemodynamic studies of untreated preeclamptic women demonstrate that hypertension in this disorder is due to systemic vasoconstriction associated with decreased cardiac output (CO) and left ventricular filling pressures.[31] Paradoxically, early in pregnancy, CO is increased more in women who subsequently develop either gestational hypertension or preeclampsia than in those who go on to uneventful normotensive pregnancies, although not so reliably as to allow prediction of these disorders. Hemodynamics diverge when hypertension becomes manifest, with further increments of CO (and low systemic vascular resistance, SVR) in women with gestational hypertension and a switch to systemic vasoconstriction and low CO in women with preeclampsia.[32] Preeclampsia is characterized not only by vasoconstrictor hypertension but also by widespread endothelial dysfunction and by evidence of increased oxidative stress. Contemporary literature has focused on larger artery dynamics and on measures of aortic stiffness, revealing marked increments of systolic augmentation index, determined by applanation tonometry, in women with preeclampsia. By contrast, augmentation index is usually negative in normal gravidas and only modestly elevated in gravidas with chronic or gestational hypertension.[33-35]

Preeclampsia decreases glomerular filtration rate (GFR) more than effective renal plasma flow (ERPF), consistent with selective afferent arteriolar renal vasoconstriction, and usually decreases renal uric acid clearance, elevating serum levels above the norms for pregnancy (2.8 to 3.2 mg/dL).[13] The older literature demonstrated striking parallels between the severity of hyperuricemia and either renal biopsy or clinical manifestations of preeclampsia,[36] and more recent studies have revisited the diagnostic and prognostic value of hyperuricemia, demonstrating that uric acid increases progressively before the onset of hypertension in women with preeclampsia and that hyperuricemia predicts fetal morbidity even in the absence of preeclampsia.[37,38] The proteinuria that characterizes preeclampsia is nonselective, with increased excretion of both albumin and nonalbumin proteins. Preeclampsia is the major cause of nephrotic-range proteinuria during pregnancy. The occurrence of edema (which is common even in normal pregnancy) is quite variable in preeclampsia; indeed, many women who present with eclamptic seizures may be free of edema.

Experts have had a longstanding controversy regarding the mechanisms that lead to eclamptic seizures and CNS complications in preeclampsia. Some have viewed these as a form of hypertensive encephalopathy, whereas others have suggested that brain injury is caused by ischemia resulting from local vasoconstriction. The latter view seems best supported by the classic autopsy series of Sheehan and Lynch,[39] which noted hemorrhage and petechiae that are likely the result of focal ischemia. By contrast, more recent studies have used noninvasive Doppler techniques to suggest a role for increased cerebral perfusion pressure in most, but not all, cases.[40] This construct leads to specific therapeutic strategies regarding selection of antihypertensive agents in preeclamptic women because labetalol and magnesium (but not vasodilators) appear to decrease elevated cerebral perfusion pressure in these patients.[41,42]

Because preeclampsia may occur in molar pregnancy (i.e., without a fetus), tends to resolve following delivery of the placenta, and seems uniformly associated with typical defects in placentation when it occurs in primigravid women without underlying risk factors, much attention has been focused on a pathophysiological role of the placenta. The currently held belief is that early abnormalities in trophoblastic invasion and remodeling of spiral arteries may fail to decrease placental resistance appropriately, leading to focal ischemia in the placenta and elaboration of factors that may act on the maternal vasculature to result in preeclampsia. A large body of literature seems to support this construct by demonstrating that experimental uteroplacental hypoperfusion leads to hypertension in pregnant laboratory animals.[43] In preeclamptic women, the placenta elaborates soluble fomesin-like tyrosine kinase-1 (sFlt-1), a soluble receptor for (and functional antagonist of) the growth factors VEGF and PlGF.[17,31] Decreased availability of these growth factors may increase BP and almost certainly leads to proteinuria and the renal biopsy lesion of glomerular endotheliosis, which is typical of preeclampsia. The preeclamptic placenta may also shed soluble endoglin, a TGF-β receptor, which may act in concert with sFlt-1.[44]

Sympathetic outflow is increased in women with preeclampsia, perhaps contributing to hypertension,[45] and preceding the onset of clinically evident disease.[46] Several

studies have also demonstrated changes in angiotensin receptor expression and activity[47] or the occurrence of autoantibodies that activate AT_1 receptors in women with preeclampsia.[17,48] The former report noted the occurrence of (bradykinin) B_2-AT_1 receptor heterodimers in maternal resistance arteries from preeclamptic women; it is conceivable that these abnormal receptors might reveal epitopes, which then lead to agonistic autoantibodies. These autoantibodies, which clear after delivery, may underlie not only vasoconstriction and hypertension, but also oxidative stress (via AT_1 receptor activation of superoxide synthesis by NAD(P)H oxidase) and endothelial dysfunction. The effect of these autoantibodies is inhibited in vitro by angiotensin receptor blockers (ARBs), but use of these agents, along with use of ACE inhibitors, is contraindicated in late pregnancy due to fetal toxicity.[49]

STRATEGIES TO PREVENT PREECLAMPSIA

Meta-analyses of antihypertensive treatment in pregnant women with chronic hypertension agree that BP control per se fails to prevent preeclampsia.[50,51] Likewise, neither salt restriction nor prophylactic diuretics prevents preeclampsia, despite earlier claims to the contrary.[52] Likewise, despite observations of hypocalciuria in preeclamptic women, several large studies of calcium supplementation failed to demonstrate significant prevention of proteinuric hypertension.[53] By contrast, although there was still no effect on the occurrence of preeclampsia, a contemporary randomized trial in 8325 nulliparous women in developing countries showed benefit to women with extremely low dietary calcium by decreasing eclampsia, severe gestational hypertension, and several composite measures of maternal morbidity.[53a]

Among many studies of circulating vasoconstrictor factors in women with preeclampsia, several suggested an imbalance in arachidonic acid metabolism, favoring vasoconstrictor thromboxanes over prostacyclin and leading to many studies of low-dose (60 to 100 mg/day) aspirin. Promising results of many early, small studies have not been confirmed in subsequent well-designed large trials that included > 25,000 women and showed only trivial effects on maternal or fetal outcome or on the occurrence of preeclampsia.[54,55] Additional studies of women at high risk for recurrent or superimposed preeclampsia (see later) also failed to demonstrate meaningful prevention of proteinuric hypertension with aspirin. Although meta-analyses of trials that included > 36,000 women have suggested some benefit (RR 0.81 [0.75 to 0.88]) of aspirin prophylaxis, this conclusion is not supported by any of the larger, well-designed trials included within the meta-analysis and have failed to identify any aspirin-sensitive subgroups of women at risk.[56] For example, in women at moderate risk for preeclampsia, aspirin was without significant effect in any of the 8 trials with > 400 women/study arm. Similarly, a single negative study accounted for 2503 of the 4222 women in the 19 trials included in the meta-analysis of aspirin trials in women at high risk for preeclampsia. It is possible that increased doses or an altered dosing schedule might reveal benefits of antiplatelet therapy, though further large studies seem unlikely.[57]

An extremely controversial literature has suggested that genetic thrombophilias including the factor V Leiden and prothrombin gene mutations may increase the risk of preeclampsia, with studies appearing to either support or refute this association.[58,59] Interestingly, a preliminary report of a large, nonrandomized case series suggested that low-molecular-weight heparin could prevent recurrent preeclampsia, especially early severe disease, in women with these thrombophilias and a history of prior preeclampsia.[60] If confirmed by a properly designed randomized controlled trial, this finding would change practice with regard to screening and secondary prophylaxis of preeclampsia.

On the basis of the increased oxidative stress that characterizes preeclampsia and could account for its vascular abnormalities, several large studies of prophylactic vitamins C and E supplementation have been completed. The first to be reported showed no benefit in 2395 women at high risk for preeclampsia.[61] Of concern, vitamin supplementation appeared to result in more severe and earlier-onset preeclampsia, more severe hypertension, lower birthweight, and increased neonatal morbidity.[61,62] A similarly large and well-designed trial has been completed in Australian nulliparas, again showing no benefit, and an even larger trial is ongoing in the United States.[62]

EVALUATION AND MANAGEMENT OF HYPERTENSION IN PREGNANCY

Evaluation of women with chronic hypertension or with a history of hypertension in a previous pregnancy should begin before conception. Evaluation should focus on the possibility of secondary hypertension, assessment of renal function and hypertensive target organ damage, detecting underlying diabetes or renal disease, and family history of pregnancy complications (Fig. 39–1). Proteinuria, per se, appears to increase pregnancy risk in hypertensive women. In addition, the obstetric history should focus on both maternal and neonatal outcome that includes premature birth, intrauterine growth restriction (IUGR) leading to small-for-gestational-age (SGA) infants, placental abruption, fetal demise, neonatal morbidity and mortality, and the severity and timing of superimposed preeclampsia.

Gestational vasodilation will allow discontinuation of all antihypertensive drugs in most women whose hypertension was well controlled using two or fewer agents before conception. Often, no antihypertensives will be required until later in pregnancy, obviating any concerns regarding drug safety in the first trimester. Women should have a baseline laboratory evaluation that includes urinalysis and urine culture, 24-hour urine for evaluation of creatinine clearance, protein and albumin excretion, comprehensive chemistry panel including measurement of transaminases, uric acid and electrolytes, and CBC with platelets. Most clinicians would repeat these studies each trimester in order to establish a new baseline to aid in the recognition of superimposed preeclampsia, although no prospective studies demonstrate benefit from this strategy. Women should then be seen every 2 to 3 weeks for measurement of BP and urine protein and for fetal assessment as indicated.

Higher-risk, chronic, hypertensive women include those with advanced maternal age, longstanding hypertension or any evidence of target organ damage, diabetes mellitus, renal disease of any cause or severity, any connective tissue disease,

Evaluation prior to conception

Rule out secondary HTN if any clinical suspicion
Screen for target organ damage (TOD)
Determine if absolute need for ACEI/ARB
- change to other med if no compelling indication,
- otherwise continue and stop as soon as pregnancy confirmed

Assess renal function and proteinuria/albuminuria
- Risk increased if pre-pregnancy Screat >1.4 m/dL

Determine if other medical comorbidities or FH that increase pregnancy risk

⇩

Pregnancy confirmed

Stop ACEI/ARB
Routine antenatal care
Evaluation by High-Risk OB specialist if not done already
If no TOD and BP<140/90, taper or D/C antihypertensives
- Consider home BP monitoring, recheck accuracy of home BP device against auscultated BP at each visit

Baseline labs (electrolytes, BUN, Creat, transaminases, uric acid, LDH, 24h urine for CrCl, protein and microalbumin, CBC, platelets)

⇩

After mid-pregnancy

Office visits at least every 2-3 wk
- Measure BP, urine prot/creat or albumin/creat ratio

Repeat baseline labs each trimester
Fetal assessment as indicated

⇩

Recurrent or worsened hypertension (>140/90)

Inpatient evaluation for signs, symptoms or lab evidence of preeclampsia
Assess fetal well-being
(Re-) start antihypertensives for BP>150/100 (lower if underlying target organ damage or nephropathy)
Parenteral antihypertensives as needed to keep BP<160/105 (see Table 39–3)

Figure 39–1 Outline of scheme for evaluation, counseling, and management of women with chronic hypertension who contemplate pregnancy and for management of superimposed preeclampsia (*next page*) should it develop in these women. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; GA, gestational age; GFR, glomerular filtration rate; TOD, target organ damage.

cardiomyopathy, vascular malformation, previous history of fetal or perinatal loss, or worsened hypertension early in pregnancy. These women require closer observation, collaborative care with appropriate subspecialists, and probably tighter BP control to avoid progressive target organ damage during pregnancy. Despite general agreement, no studies have shown benefit of tighter BP control in hypertensive gravidas with renal disease or other underlying medical disorders. Worsened hypertension or suspicion of superimposed preeclampsia will commonly lead to inpatient evaluation in order to assure maternal and fetal well-being, titrate antihypertensive therapy, and decide whether pregnancy may be prolonged safely with close monitoring.

Antihypertensive Therapy Remote from Delivery

With some small differences, the American, Canadian, and Australia–New Zealand consensus statements recognize methyldopa as a preferred antihypertensive with the greatest experience in pregnancy.[2,8,9] It is well tolerated by pregnant women, does not alter uteroplacental or fetal hemodynamics, and has the best long-term follow-up of childhood development following exposure in utero, albeit in an underpowered study.[63] Methyldopa-induced hepatitis is a rare adverse effect, and Coombs-positive hemolytic anemia is rare with short-term treatment, though many women cannot tolerate its common adverse effects of drowsiness or dry mouth. Some concern followed a meta-analysis along with a large retrospective single center report suggesting that other antihypertensive drugs might be superior to methyldopa in limiting perinatal morbidity and mortality.[51,64] However, adequately powered prospective comparative trials are lacking and should be required before abandoning the long clinical experience and consensus support for use of methyldopa in pregnancy.

β-Blockers are also widely used in pregnancy, have been assessed in several randomized trials, and are the subject of a Cochrane meta-analysis.[50] Early preclinical and clinical observations raised concerns of impaired uteroplacental perfusion, fetal growth restriction, and harmful cardiovascular effects on the fetus. Early use of atenolol in one trial led to striking fetal growth restriction, a conclusion supported by several reviews, retrospective series, and meta-analyses.[65-67] However, most prospective studies, focusing on β-blocker use in the third trimester, have shown effective BP control, prevention of more severe hypertension, and an absence of significant adverse effects including bradycardia on the fetus. A large single-center case series has noted superior perinatal outcome with β-blockers (primarily atenolol) compared with other agents (primarily nifedipine or methyldopa).[64] Further, a meta-analysis of several small trials suggested that β-blockers might decrease (and calcium channel blockers increase) the

Clinical diagnosis of preeclampsia
Parenteral antihypertensives as needed to keep BP<160/105 (see Table 39–3)
Magnesium sulfate for eclampsia, or for initial care of severe PE, especially when delivery is imminent
(Adjust dosing when GFR is low)

If GA≥38 wk: Deliver

Deliver if GA<23 wk or ≥34 wk AND any of the following:
- Severe preeclampsia (see Table 39–4)
- Labor or ruptured membranes
- Suspected placental abruption
- Non-reassuring fetal testing
- Severe oligohydramnios or fetal growth restriction

If severe PE at GA 23-32 wk:
- Steroids for fetal lung maturation
- Inpatient care with >daily evaluation of mother and fetus
- Oral antihypertensives (see Table 39–2)
- Plan to deliver at 34 wk

If severe PE at GA 33-34 wk:
- Steroids for fetal lung maturation
- Inpatient evaluation and antihypertensives as above
- Delivery after 48-72 hr

Mild PE at GA <38 wk:
- Inpatient or office management
- Oral antihypertensives for BP >150/100
- Daily BP measurement and assessment for ominous symptoms
- Physical exam, lab evaluation, fetal assessment 2x/wk
- Deliver if worsening maternal or fetal condition, onset of labor, or when GA ≤38 wk

Figure 39–1, cont'd

incidence of proteinuria or superimposed preeclampsia, perhaps by limiting abnormal elevations in cardiac output.[68] The latter preliminary observation should provoke further study rather than a change in practice.[51] Although many older studies focused on agents such as atenolol, the NHBPEP Working Group advocates labetalol (a combined α- and β-blocker) as an alternative to methyldopa, and the Australasian group advocates use of β-blockers with intrinsic sympathomimetic activity, such as oxprenolol (not available in the United States) or pindolol.[8]

Calcium channel blockers, principally extended-release nifedipine, are widely used, apparently safe, and effective in pregnancy.[2] Although data are limited, nifedipine is widely viewed as an acceptable alternative to methyldopa or β-blockers for chronic use during pregnancy.

Hydralazine has been the most commonly used second-line agent (following combinations of those discussed earlier). It is used in combination with either a β-blocker or methyldopa to limit reflex tachycardia. Use of α-adrenergic blockers other than in the setting of suspected pheochromocytoma seems to have little basis. Diuretic use during pregnancy is controversial. Diuretics limit normal gestational volume expansion and can decrease amniotic fluid volume and lead to electrolyte abnormalities. However, they do not seem to impair fetal outcome. Diuretics may be continued if they were crucial to BP control before conception and may be combined with other agents, especially in patients with renal insufficiency, heart disease, or when clinical volume overload is a problem. Diuretics are not used when preeclampsia is suspected because its hemodynamics are characterized by decreased cardiac output and primary systemic vasoconstriction.[12,32]

Increased circulating elements of the renin-angiotensin system during pregnancy and evidence for AT_1 receptor activation in preeclampsia might seem to support use of ACE inhibitors or AT_1 receptor blockers in hypertensive gravidas. These drugs are now widely used for renal protection in young women of childbearing age who have underlying diabetic nephropathy or proteinuric renal disease. They are, however, contraindicated during the latter half of pregnancy due to a specific fetopathy (including renal dysgenesis and calvarial hypoplasia) and the risk of (fatal) neonatal acute renal failure.[49,69,70] ACE inhibitors and AT_1 receptor blockers are often discontinued when pregnancy is planned. However, because they are not teratogenic and all adverse outcomes appear caused by fetal exposure in the second or third trimester, reliable patients who are followed closely can continue these drugs through conception, discontinuing them in the first trimester if pregnancy is detected early. Table 39–2 summarizes those agents most commonly used for chronic BP control in pregnancy.

Antihypertensive Therapy of More Severe Hypertension

Table 39–3 lists the antihypertensives most commonly used for urgent control of severe hypertension late in pregnancy. Hydralazine is used either in small (5- to 10-mg) repeated doses or as a continuous infusion because larger doses or

Table 39–2 Oral Antihypertensives Used Commonly in Pregnancy

Drug (FDA Risk*,†)	Dose	Concerns or Comments
Most Commonly Used First-Line Agents		
Methyldopa (B)	0.5-3.0 g/d in 2-3 divided doses	Preferred agent of the NHBPEP working group; maternal side effects sometimes limit use.
Labetalol (C) or other β-receptor antagonists	200-2400 mg/d in 2-3 divided doses	Labetalol is preferred by the NHBPEP working group as an alternative to methyldopa. Atenolol most commonly used in Canada and β-blockers with intrinsic sympathomimetic activity are preferred by some in Australia. May cause fetal growth restriction when started early.
Nifedipine (C)	30-120 mg/d of a slow-release preparation	Less experience with other calcium entry blockers.
Adjunctive Agents		
Hydralazine (C)	50-300 mg/d in 2-4 divided doses	Few controlled trials, long experience; used only in combination with sympatholytic agent (e.g., methyldopa or a β-blocker) to prevent reflex tachycardia.
Thiazide diuretics (C)	Depends on specific agent	Most studies in normotensive gravidas.
Contraindicated		
ACE inhibitors and AT1 receptor antagonists (D[4])		Use after first trimester can lead to fetopathy; oligohydramnios; growth retardation; and neonatal anuric renal failure, which may be fatal.

*No antihypertensive has been proven safe for use during the first trimester (i.e., FDA Category A).
†U.S. Food and Drug Administration classifies the risk for most agents as C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should only be given if the potential benefit justifies the potential risk to the fetus. This classification is of limited clinical utility since it unfortunately still applies to most drugs used during pregnancy.
NHBPEP, National High Blood Pressure Coordinating Committee.

Table 39–3 Antihypertensives Commonly Used for Urgent BP Control

Drug (FDA Risk*)	Dose and Route	Concerns or Comments†
Hydralazine (C)	5 mg, IV or IM, then 5-10 mg every 20-40 min; or constant infusion of 0.5-10 mg/hr	Preferred by NHBPEP working group. Higher doses or more frequent administration often precipitate maternal or fetal distress, which appear more common than with other agents.
Labetalol (C)	20 mg IV, then 20-80 mg every 20-30 min, up to maximum of 300 mg; or constant infusion of 1-2 mg/min	Probably less risk of tachycardia and arrhythmia than with other vasodilators; likely less BP control than hydralazine.
Nifedipine (C)	5-10 mg PO, repeat in 30 min if necessary, then 10-20 mg every 2-6 hr	Parenteral calcium channel blockers (e.g., nicardipine is a reasonable alternative, but fewer data are available).

*U.S. Food and Drug Administration Class C, as noted in footnote to Table 39–1.
†Adverse effects for all agents, except as noted, may include headache, flushing, nausea, and tachycardia (primarily due to precipitous hypotension and reflex sympathetic activation).

frequent dosing may lead to precipitous maternal hypotension and fetal distress. Parenteral labetalol, by continuous IV infusion or in repeated boluses, has replaced hydralazine at many centers and appears to have similar safety and efficacy, although comparative studies are few and parenteral labetalol may result in less effective BP control.[71,72] Despite its lack of approval by the U.S. Food and Drug Administration for the treatment of hypertension, the NHBPEP Working Group advocates oral (or sublingual) nifedipine as an acceptable alternative to hydralazine or labetalol for urgent BP control during pregnancy.[2] Its efficacy and safety appear similar to the other agents, whereas diazoxide and ketanserin seem inferior.[71] Although most studies have suggested little difference in outcome among patients treated with these three agents, a meta-analysis suggests that hydralazine may be inferior to labetalol or calcium channel blockers because it more often leads to adverse effects including excessive hypotension, fetal distress, oliguria or renal dysfunction, placental abruption, and cesarean delivery due to toxicity.[72] Sodium nitroprusside remains a relatively contraindicated agent of last resort, usually reserved for urgent BP control in the minutes leading up to delivery.[73] Finally, although there have been reports of ACE inhibitor use as salvage therapy during pregnancy,[74] there seems to be no justification for use of these agents or of

angiotensin receptor blockers during the second or third trimester.

Clinical and Adjunctive Management of Preeclampsia

Suspicion of preeclampsia should lead to hospitalization and inpatient evaluation (see Fig. 39–1). Despite common practice, we still do not know if hypertensive gravidas benefit from bedrest.[75] Near to term (>34 weeks), if fetal maturity can be assured, delivery is the preferred and definitive treatment for preeclampsia. Earlier in pregnancy, it may seem desirable to temporize, attempting to control BP; administer glucocorticoids to hasten fetal lung maturation; and monitor laboratory and clinical status closely so as to prolong pregnancy. The obstetric literature on such temporizing strategies often appears confusing and contradictory. Expectant management may result in a few days to, rarely, several weeks of additional fetal maturation; however, such strategies are best reserved to tertiary centers. Regardless of gestational age, any of the ominous signs or symptoms noted in Table 39–4 should lead to immediate delivery. As noted earlier, accelerated hypertension should be treated at systolic levels of > 160 mm Hg or diastolic of > 105 mm Hg (Korotkoff 5) to avoid the cerebrovascular catastrophes that can occur at pressures of ≥170/110. We advocate treatment at these somewhat lower pressures due to increased BP lability and uncertainty in BP measurement in women with preeclampsia. Central nervous system signs or symptoms including even headache or blurred vision should provoke treatment at even lower pressures. Despite findings from invasive hemodynamic studies, there appears to be no benefit from therapeutic volume expansion in addition to BP control.[76]

Parenteral magnesium sulfate has long been favored by North American clinicians for prevention or treatment of eclamptic seizures, which can occur antepartum (38% to 53% of cases), intrapartum (18% to 36% of cases), or postpartum (11% to 36% of cases).[77] Magnesium is more effective than either phenytoin or diazepam in preventing recurrent seizures in women with eclampsia.[78,79] Several primary prevention trials in women with preeclampsia including a placebo-controlled, double-blind study in more than 10,000 women, demonstrated the efficacy of magnesium, without significant short-term adverse effects to mother or baby.[77,80] It remains unclear, however, which women with preeclampsia should be offered magnesium and for how long. In most centers, treatment usually entails a loading dose of 4 to 6 g $MgSO_4$ (infused over 10 minutes, never as a bolus), followed by continuous infusion of 1 to 2 g/hour to achieve plasma levels of 5 to 9 mg/dL. Magnesium is then usually continued until the patient stabilizes or for 24 hours following delivery. Lower doses should be used, without continuous infusion, guided by serum levels, in women with any degree of renal insufficiency because magnesium is excreted renally. Finally, a vial of calcium gluconate should always be kept at the bedside in case of magnesium toxicity.

Table 39–4 Ominous Signs and Symptoms in Preeclampsia Suggesting Prompt Delivery

Inability to control BP (systolic < 160 mm Hg or diastolic < 105)
Any evidence of acute renal failure or progressive oliguria
Falling platelets or thrombocytopenia < 10^5/mm^3
Any evidence of microangiopathic hemolysis or coagulopathy
Upper abdominal (epigastric or right upper quadrant) pain
Headache, visual disturbance, or any CNS signs
Retinal hemorrhage or papilledema
Acute congestive heart failure or pulmonary edema

Overall, our clinical approach to evaluation, management, and treatment of pregnant women with underlying hypertension is in accord with recommendations made by the NHBPEP Working Group (see Fig. 39–1).[2] Our key objectives, to be carried out in close coordination with experienced high-risk obstetric colleagues, are to achieve BP control adequate to assure maternal safety; carefully and serially monitor maternal BP, well-being, and laboratory data in order to assist early recognition of superimposed preeclampsia; and proceed to expeditious delivery (±magnesium prophylaxis) in the face of preeclampsia or accelerated hypertension when it presents a threat to maternal safety.

Postpartum Antihypertensive Therapy in Nursing Mothers

Despite a clear understanding of the pharmacokinetic principles governing drug distribution to milk and delivery to the infant,[81] there are few well-designed studies assessing neonatal effects of administered antihypertensive drugs in nursing mothers. However, this field has been summarized thoughtfully in a current review.[82] Factors that favor drug passage into milk are a small maternal volume of distribution, low plasma protein binding, high lipid solubility, and lack of charge at physiological pH. Even when drugs are ingested by nursing infants, effective infant exposure depends on the volume of milk ingested, intervals between drug administration and nursing, oral bioavailability (in the infant), and the capacity of the infant to clear the drug.

Neonatal exposure to methyldopa, propranolol, or labetalol appears low and is considered safe. Similarly, calcium channel blockers, although transferred into milk, appear to be safe for nursing infants. By contrast, atenolol and metoprolol are concentrated in breast milk. Diuretics are believed to decrease milk production so as to interfere with nursing, though convincing studies are lacking. Due to concerns regarding effects of ACE inhibitors and AT_1 receptor antagonists on neonatal renal function, these drugs are usually avoided, especially in very premature infants. However, milk concentrations of captopril are undetectable, suggesting use of this agent when an ACE inhibitor is required.[83]

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Management of Hypertension in Children and Adolescents

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CHAPTER CONTENTS

INTRODUCTION

Hypertension can occur at any phase of childhood, from the newborn period through adolescence. Hypertension in childhood is defined differently than in adulthood and occurs less frequently than in adults. The underlying causes of hypertension are identified more frequently in children than in adults. Childhood hypertension also has some striking similarities to hypertension in adults. Severe, untreated hypertension in children has as poor an outcome as it does in adults.[1] Children with essential hypertension can have the same risk factors for cardiovascular disease as adults; and children with hypertension can benefit from interventions to control the blood pressure (BP). The diagnosis of hypertension requires BP measurements, systolic or diastolic, or both, that are consistently equal to or above the 95th percentile for age, sex, and height.[2] With this statistical definition, the prevalence of hypertension is expected to be 1% to 5%. As more attention is given to evaluating BP in children during routine health care visits, and as a result of the rising rates of childhood obesity, more cases of hypertension in the young are being identified. An important aspect in the management of high BP in the young is to determine when elevated BP is a sign of an underlying disease, as with secondary hypertension; and when elevated BP in childhood is an early expression of primary (essential) hypertension.

DEFINITION OF HYPERTENSION IN CHILDHOOD

- Normotension: Systolic and diastolic BP <90th percentile.
- Prehypertension: Systolic or diastolic BP >90th percentile and <95th percentile (for adolescents >120/80 mm Hg and <95 percentile).
- Stage 1 hypertension: Systolic or diastolic BP, or both, between the 95th percentile and 5 mm Hg above the 99th percentile.
- Stage 2 hypertension: Systolic or diastolic BP, or both, >5 mm Hg above the 99th percentile.

The definition of hypertension in adults is based on the level of BP that is linked with an increase in risk for cardiovascular events. Although the risk for cardiovascular events in adults increases as BP rises above 115/75 mm Hg,[3] hypertension continues to be defined as BP that exceeds 140/90 mm Hg, regardless of age or gender. However, in children, with the exception of extreme hypertension as noted earlier, no data have linked a level of BP with subsequent cardiovascular events. In the absence of such data, hypertension is defined statistically. The results of several large epidemiologic studies that measured BP in healthy children[2,4-6] provide data from which the normal distribution of BP in healthy children and adolescents in the United States has been established.[2] An analysis of BP data on healthy children in Europe describes a similar BP distribution pattern.[7,8]

A progressive rise in BP occurs with increasing age throughout childhood concurrent with the normal age-related increase in height and weight. Thus, there is a consistent relationship of BP with body size in childhood; and there is a normal upward shift in BP with growth. A gender difference in BP distribution emerges in adolescence that is concurrent with a gender difference in height.

The definition of hypertension in children delineates the top segment of the normal BP distribution at each childhood age.[2,4] With the expansion of the epidemiologic data and with further analysis of the growth-related determinants of BP in childhood, the 95th percentile is further adjusted for height.[2,6] The present definition of hypertension in children and adolescents is systolic or diastolic BP that, on repeated measurement, is equal to or greater than the 95th percentile for age, sex, and height. The severity of hypertension is also defined according to the degree of BP elevation. Table 40–1 provides the level of BP for the 90th, 95th, and 99th percentiles for age, sex, and height percentile for boys, and Table 40–2 provides the same percentile levels for girls.[2] In each table the 50th percentile for systolic and diastolic BP is also provided to denote the midpoint of the BP distribution.

Table 40–1 Blood Pressure Levels for Boys by Age and Height Percentiles

Age (Yr)	BP Percentile ↓	Systolic BP (mm Hg) ← Percentile of Height →							Diastolic BP (mm Hg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92

Continued

Table 40–1 Blood Pressure Levels for Boys by Age and Height Percentiles—cont'd

Age (Yr)	BP Percentile ↓	Systolic BP (mm Hg) ← Percentile of Height →							Diastolic BP (mm Hg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure.

Table 40–2 Blood Pressure Levels for Girls by Age and Height Percentiles

Age (Yr)	BP Percentile ↓	Systolic BP (mm Hg) ← Percentile of Height →							Diastolic BP (mm Hg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87

Table 40–2 Blood Pressure Levels for Girls by Age and Height Percentiles—cont'd

Age (Yr)	BP Percentile ↓	Systolic BP (mm Hg) ← Percentile of Height →							Diastolic BP (mm Hg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure.

MEASUREMENT OF BLOOD PRESSURE IN THE YOUNG

Measurement of BP in children and adolescents should be performed in a standardized manner that is similar to the methods used in developing BP tables. In the ambulatory clinic setting the preferred method for BP measurement in children is by auscultation with a standard sphygmomanometer. Detailed guidelines for BP measurement in the young have been published.[2,9] Correct BP measurement in children requires the use of a cuff that is appropriate for the size of the child's upper arm. A cuff that has a bladder width approximately 40% of the arm circumference midway between the olecranon and the acromion should be selected because it usually covers 80% to 100% of the arm's circumference. Most manufacturers of BP cuffs provide lines on the cuff that are useful in choosing the correct cuff size for a given child. The equipment necessary to measure BP in children 3 years of age through adolescence includes three pediatric cuffs of different size, as well as a standard adult cuff, an oversized cuff, and a thigh cuff for leg BP measurement. The latter two cuffs may be necessary for use in obese adolescents.

BP measurement in children should be conducted in a quiet and comfortable environment after 3 to 5 minutes of rest according to a procedure similar to that described for adults.[9] With the exception of acute illness, the BP should be measured with the child in the seated position with the cubital fossa supported at heart level. The child should have his or her feet on the floor while the BP is measured, rather than dangling the feet from an examination table. Overinflation of the cuff should be avoided due to discomfort, particularly in younger children. The BP should be measured and recorded at least twice on each occasion. The disappearance of Korotkoff sounds or fifth Korotkoff sound (K5) is the definition of diastolic pressure in adults. In children, particularly preadolescents, a difference of several mm Hg is frequently present between the fourth Korotkoff sound, the muffling of Korotkoff sounds, and K5.[10] Normative BP data in children indicate that K5 can be used as the measure of diastolic BP in children, as well as adults. When there is a large gap between K4 and K5, both numbers should be recorded.

The BP level in a child is interpreted by comparing the child's measured BP with the BP tables. Precise interpretation requires plotting the BP according to the child's height percentile, as well as age and sex. The child's height is measured and plotted on the standard child growth curves. The height percentile is used in the tables, wherein the BP level for the 90th and 95th percentiles at the child's age, sex, and height percentile are compared with the child's measured BP. Tables 40–1 and 40–2, which contain the BP levels for the 50th, 90th, 95th, and 99th percentiles according to sex, age, and height, are from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents,[2] (*www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm*). A program can be downloaded from this site to provide a classification of a child's BP status when his or her sex, age, height, and BP are entered.

Elevated BP measurements in a child or adolescent must be confirmed on repeated visits before making the diagnosis of hypertension. An average of multiple BP measurements taken over weeks or months provides a more accurate characterization of an individual's BP level. Population standards for ambulatory BP monitoring (ABPM) over a 24-hour period in children and adolescents are now available,[11] and ABPM BP data can be helpful in making clinical decisions in these patients.[12] ABPM can be used to detect "white coat hypertension," determine the need for pharmacologic therapy, and assess the effectiveness of therapeutic interventions. When ABPM is used in children or adolescents, the appropriate cuff size should be used and the appropriate childhood BP cutpoints should be used for interpretation of the results.

CAUSES OF HYPERTENSION IN THE YOUNG

The management strategies for hypertension in a child or adolescent are determined by the underlying cause of the hypertension—that is, whether the hypertension is primary (or essential) or whether the hypertension is secondary to some other cause. If the hypertension is secondary, the management will be determined by the underlying disorder that is causing high BP. For example, the management of a child with hypertension secondary to chronic glomerulonephritis would be antihypertensive medication that would lower BP and also possibly confer renal protection. Alternatively, the management for a child with hypertension secondary to hyperthyroidism would be to correct the hyperthyroidism, as well as control the BP with antihypertensive medication until the child is euthyroid.

Secondary Hypertension

Although hypertension is, overall, less prevalent in children than adults, hypertension that is secondary to an underlying renal or endocrine disorder is more frequently found in hypertensive children than in hypertensive adults. The prevalence of secondary hypertension in the young varies according to the age and severity of hypertension. Hanna et al.[13] identified a secondary cause of hypertension in 90% of children younger than 10 years of age; only 10% of these young children were considered to have essential hypertension. A report on a series that included both children and adolescents with hypertension describes secondary hypertension in 65% of the adolescents, with 35% of the adolescents having essential hypertension.[14] With the increase in attention to BP levels in the young, along with the rising rates of childhood obesity, the proportion of children and adolescents with essential hypertension is increasing.

Young children, younger than 12 years of age, with sustained hypertension are more likely to have a secondary cause for the hypertension. The degree of hypertension is also an important clue, as severe BP elevation in a young child is most likely to be due to an underlying abnormality. Children and adolescents with stage 2 hypertension should have a thorough evaluation for possible causes of the hypertension and for evidence of target organ damage. Although the list of conditions that can cause hypertension in the young is long, the majority of the identifiable causes of hypertension in the young are related to renal disorders. Table 40–3 provides a list of underlying causes for chronic hypertension in the young, as well as the conditions associated with acute hypertension in the young.

For children up to 10 years of age, the leading causes of hypertension are renal parenchymal diseases, coarctation of the aorta, and renal artery stenosis. Coarctation of the aorta, a congenital cardiac anomaly that can be missed in infants and toddlers, should be considered in a hypertensive child.[15-17] The disorders that cause acute hypertension include postinfectious glomerulonephritis and hemolytic uremic syndrome. Some conditions, such as hemolytic uremic syndrome, may cause permanent renal scarring that results in chronic hypertension.

The secondary causes of hypertension that are detected most frequently in adolescents are renal parenchymal diseases, such as chronic pyelonephritis, focal segmental glomerulosclerosis (FSGS), and other types of chronic glomerulonephritis. Adolescent behaviors that may contribute to high BP are use of illicit substances, especially cocaine and amphetamine-related compounds.[18,19] Other substances that have been associated with high BP in adolescents include appetite suppressants (both prescription and over the counter), oral contraceptives, excessive alcohol intake, and use of anabolic steroids for body building.[20]

Essential Hypertension

Essential hypertension has traditionally been considered a disorder of older adults. However, the concept that essential hypertension has its roots in childhood can be inferred from BP tracking data, which demonstrate that children with elevated BP will continue to have elevated BP as adults.[6] Evidence of target organ injury is detectable in children and adolescents with essential hypertension, even with mild degrees of BP elevation. Using echocardiography and appropriate childhood reference values for cardiac structure, left ventricular hypertrophy (LVH) has been reported in 30% to 40% of children and adolescents with hypertension.[21,22] Available longitudinal data support a direct link between risk factors in childhood including BP level, with evidence of target organ injury including greater intima-media thickness of carotid arteries.[21,23,24] Therefore, essential hypertension in childhood should be considered an early phase of a chronic disease.

Children and adolescents with essential hypertension generally demonstrate several clinical characteristics or asso-

Table 40–3 Secondary Causes of Hypertension

Chronic Hypertension	
Renal	**Drugs**
Chronic glomerulonephritis	Corticosteroids
Interstitial nephritis	Alcohol
Collagen vascular diseases	Appetite suppressants
Reflux nephropathy	Anabolic steroids
Polycystic kidney disease	Oral contraceptives
Medullary cystic disease	Nicotine
Hydronephrosis	**Syndromes**
Hypoplastic/dysplastic kidney	Alport
Cardiac and Vascular	Williams (renovascular lesions)
Coarctation of aorta	Turner (coarctation or renovascular)
Renal artery stenosis	Tuberous sclerosis (cystic renal)
Takayasu arteritis	Neurofibromatosis (renovascular)
Endocrine	Adrenogenital
Hyperthyroidism	Little
Pheochromocytoma	
Primary aldosteronism	
Acute Hypertension	
Renal	**Drugs**
Postinfectious glomerulonephritis	Cocaine
Schönlein-Henoch purpura	Phencyclidine
Hemolytic uremic syndrome	Amphetamines
Acute tubular necrosis	Jimson weed
Vascular	**Miscellaneous**
Renal or renal vascular trauma	Burns
Neurogenic	Orthopedic surgery
Increased intracranial pressure	Urologic surgery
Guillain-Barré syndrome	

ciated risk factors. The degree of BP elevation is generally mild, approximating the 95th percentile, and there is often considerable variability in BP over time. A consistent clinical observation in children exhibiting mild essential hypertension is a positive history of hypertension in parents or grandparents, or both.[25-27]

In both children and adults, greater body weight and increases in body weight correlate with higher BP.[28] Essential hypertension in children is frequently associated with obesity, which appears to be a contributory factor because even a modest reduction in excess adiposity is often associated with a reduction in BP.[29,30] The cluster of modest BP elevation, positive family history of hypertension, and obesity is a typical pattern in children and adolescents with essential hypertension.[31]

The prevalence of childhood obesity is increasing,[32] having more than doubled in the past 20 years.[33] An analysis of two separate sets of data from the National Health and Nutrition Examination Survey demonstrated a small but statistically significant increase in the childhood BP level that is largely due to the concurrent increase in obesity.[34] Obesity has an adverse effect on risk for cardiovascular disease and warrants attention for disease prevention and health promotion. Marked BP sensitivity to sodium intake has been demonstrated in obese adolescents, with a significant dampening in the BP response to sodium following weight reduction.[29,30] LVH can be detected in up to 40% of obese children with high BP.[35]

The term *metabolic syndrome,* or *insulin-resistance syndrome,* has been applied to the condition in which high BP, non–insulin-dependent diabetes mellitus or prediabetes, atherosclerosis, and obesity coexist (see Chapter 38). The metabolic syndrome is associated with marked increases in risk for cardiovascular events in individuals and in populations.[36] Children and adults may exhibit characteristics of the metabolic syndrome.[37-39] Some investigators have detected the metabolic syndrome in nonobese offspring of hypertensive parents,[40,41] indicating a hereditary component of the syndrome. The characteristics of the metabolic syndrome are also congruent with the overweight child having a strong family history of hypertension or early heart disease and stage 1 hypertension.[42] Although these children are not at risk for immediate adverse effects of the higher than normal BP, they should be considered at high risk for future cardiovascular disease.[43] They can benefit from behavioral changes that improve insulin action including an increase in physical activity, diet modifications, and control of excess adiposity.

EVALUATION OF HYPERTENSION IN CHILDREN AND ADOLESCENTS

- Evaluate for identifiable cause
- Evaluate for comorbidities
- Evaluate for target organ damage

When sustained hypertension is established in a child by repeated BP measurements that are at or above the 95th percentile, additional evaluation is necessary. The extent of the

diagnostic evaluation is determined by the type of hypertension that is suspected. When a secondary cause is considered, more extensive evaluation may be necessary. On the other hand, when the patient's elevated BP is more likely to be an early expression of essential hypertension, a few diagnostic screening studies may be sufficient. Children or adolescents with severe hypertension, particularly young children, generally have an identifiable underlying cause. The recommendations for evaluation of hypertension in children now include (1) evaluation for an identifiable cause; (2) evaluation for comorbidity; and (3) evaluation for target organ damage.[2]

The medical history and physical examination are basic tools in determining whether the characteristics of a patient's presentation indicate essential hypertension or reflect a secondary, and potentially correctable, cause. A particular symptom complex revealed in the history or findings on physical examination may also prompt a thorough investigation. Any pediatric patient who is hypertensive and is not growing normally should undergo an evaluation for secondary causes. A sudden onset of elevated BP in a previously normotensive child should always prompt a search for secondary causes. Absence of a positive family history of hypertension should increase the level of suspicion for an underlying disorder. A general rule is: The younger the child and the higher the BP, the more likely there will be a secondary cause of the hypertension.

Children and adolescents with essential hypertension generally have modest elevations in BP, a strong family history of essential hypertension, elevated resting heart rate, variable BP readings on repeated measurement, and obesity. If no other abnormalities are found on history or physical examination, these children require less extensive evaluation for an underlying disorder than those in whom secondary causes are suspected. However, children with early expression of essential hypertension, particularly those who are obese, may have associated comorbidities including dyslipidemia, sleep apnea, and prediabetes. These comorbidities deserve treatment because they contribute to cardiovascular disease risk.

Medical History

The medical history and physical examination are used to detect clues to determine if the BP elevation is secondary or primary and long-standing or of acute onset. The family history is particularly important. A history of essential hypertension, myocardial infarction, stroke, renal disease, diabetes, and obesity should be sought in both first- and second-degree relatives. Early onset of any of these conditions in relatives is relevant to the diagnostic evaluation of a hypertensive child. Parents should be asked about family history of heritable conditions that have hypertension as a component (e.g., polycystic kidney disease, neurofibromatosis, pheochromocytoma). Another familial type of hypertension is glucocorticoid-remediable aldosteronism, an autosomal dominant condition that should be considered when multiple family members have early-onset hypertension associated with hypokalemia or stroke.[44,45]

Details about previous health problems, such as history of urinary tract infections, is important, because there may be associated reflux nephropathy, renal scarring, and resultant hypertension. A history of medications and over-the-counter products used can be helpful.[46,47] Information should be obtained about health-related behaviors, such as usual diet, amount of physical activity or athletic participation. Use of "street" drugs, smokeless tobacco, oral contraceptive pills, cigarette smoking, diet aids, ethanol, and anabolic steroids should be queried in adolescents.

Physical Examination

The physical examination of a hypertensive child should include an assessment of the child's growth rate and body size. Weight, height, and body mass index (BMI) should be plotted according to age and sex on the child growth charts. Abnormalities in growth associated with hypertension can be seen with chronic renal disease; hyperthyroidism (causing primarily systolic hypertension); pheochromocytoma; adrenal disorders; or certain genetic abnormalities, such as Turner syndrome.

To rule out coarctation of the aorta, the BP should be measured in the leg with an appropriately sized cuff. Normally the BP level measured in the leg is slightly higher than the arm BP. A child with coarctation will have systolic hypertension in an upper extremity, sometimes absent or decreased femoral pulses, and a leg BP that is lower by 10 mm Hg or more than the BP level in the arm.[15,17]

Other physical clues to a secondary etiology for child hypertension include abnormal facies or dysmorphic features, which may suggest a variety of syndromes.[48] For example, both Turner and Williams syndromes are associated with renovascular or cardiac lesions that cause hypertension. Renal vascular lesions may cause audible abdominal bruits. Skin lesions are sometimes the first manifestations of disorders, such as tuberous sclerosis and systemic lupus erythematosus. Acanthosis nigricans in overweight children may be a sign of abnormal glucose tolerance.

Diagnostic Testing

When the history and physical examination provide clues for a specific underlying cause for the hypertension, subsequent testing should be directed to the area of clinical suspicion. In the absence of specific clues, renal parenchymal disease should be considered because it is the most frequent cause of secondary hypertension in the pediatric population. Screening studies for renal abnormalities include urinalysis, electrolytes, creatinine, complete blood count, urine culture, and renal ultrasound. Evaluation for comorbidity includes fasting plasma lipids for dyslipidemia; a sleep history for sleep apnea; and, if there is a positive family history of diabetes, a glucose tolerance test.

The evaluation also includes an assessment of target organ injury. The presence of target organ injury provides a measure of chronicity and severity (characteristics sometimes difficult to ascertain from the history) and will aid in deciding whether pharmacologic therapy should be instituted. Chest x-ray and ECG are not sufficiently sensitive to detect LVH in children and adolescents; echocardiography is a sensitive means of quantifying left ventricular mass (LVM) and detecting interventricular septal and posterior ventricular wall thickening. To adjust for differences in body size, echocardiographic measurements of LVM must be indexed to some body size measurement, such as height, weight, or body mass index. Height in meters ($m^{2.7}$) is the recommended measurement for

adjustment of echo-measured LVM to derive a left ventricular mass index (LVMI). LVMI >51 g/m$^{2.7}$ is the adult criterion for LVH. Using this criterion, one study found that 15.5% of hypertensive children have LVH.[35] However, as with BP level, the adult criteria for categorical classification are not appropriate for children and adolescents. The 95th percentile for LVMI in children and adolescents (based on normative data) is 36.88 g/m$^{2.7}$ for females and 39.36 g/m$^{2.7}$ for males.[49] When the 95th percentile for LVMI was used as the criteria for LVH in a multicenter study of hypertensive children, 41.1% of the children had LVH. In addition, LVH was detected more frequently among those who were obese. For clinical purposes, LVMI above 40 g/m$^{2.7}$ may be considered evidence of target organ damage in a child or adolescent with hypertension.

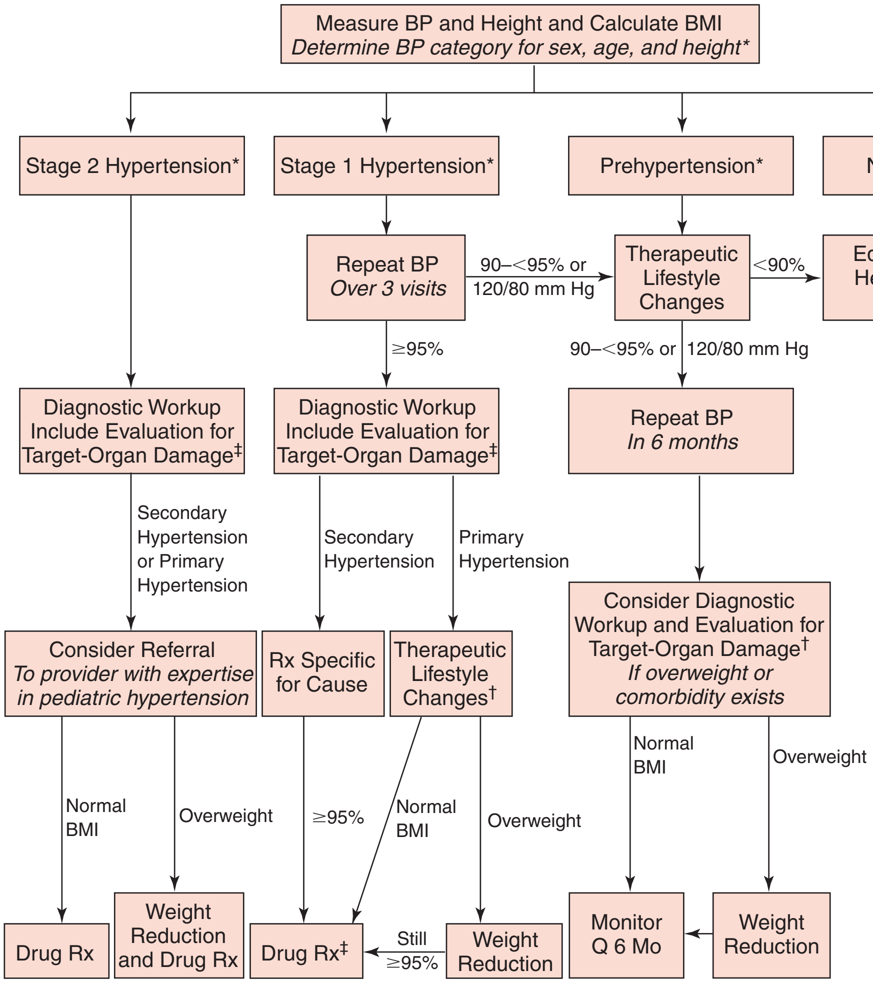
An ophthalmologic examination of retinal vessels may also be helpful in detecting signs of hypertensive vascular injury.[50] The usefulness of microalbuminuria, sometimes used as a marker for renal injury in adults,[51] has not been determined for children. The remainder of the evaluation should be directed by specific findings on history and physical examination, as well as results of initial screening studies. Laboratory or ultrasound abnormalities that suggest underlying renal disease will require more specific diagnostic testing. Electrolyte abnormalities may point to a need for further plasma renin and aldosterone testing and imaging studies.

MANAGEMENT OF HYPERTENSION IN CHILDREN AND ADOLESCENTS

An algorithm for the evaluation and treatment of hypertension in the young is provided in Figure 40–1. The algorithm takes into account the age of the child, severity of the hypertension, and presence or absence of obesity.

Normotensive

No intervention is necessary. The BP should be remeasured at the next scheduled physical examination. The child and his or her parent should be encouraged to maintain or develop healthy lifestyles including appropriate levels of physical activity, heart-healthy diets, and avoidance of excessive weight gain.



BMI, body mass index; BP, blood pressure; Rx, prescription; Q, every.
*See Tables 40–1 and 40–2. (See page 702 for definitions of hypertension in childhood).
†Diet modification and physical activity.
‡Especially if younger, very high BP, little or no family history, diabetic, or other risk factors.

Figure 40–1 Evaluation and treatment of hypertension in the young.

Prehypertensive

Pediatric patients with prehypertension should have their BP rechecked in 6 months. Therapeutic lifestyle changes (TLCs) are appropriate and may lower BP or reduce further rise in BP. The major components of TLCs—physical activity, diet modification, and weight control—should be strongly encouraged, particularly when the prehypertensive child is also obese. Further evaluation for comorbidity and target organ damage may be indicated in some children with prehypertension. A pediatric patient with prehypertension and obesity already has two components of the metabolic syndrome and should be evaluated for other comorbidities including abnormal levels of plasma lipids. An obese prehypertensive child with a strong family history of type 2 diabetes or acanthosis nigricans should also have an evaluation of glucose metabolism. When multiple risk factors are detected in an obese prehypertensive child, an echocardiogram can be helpful in determining further management. Children with chronic renal disease or diabetes mellitus, both types 1 and 2, who have BP levels in the prehypertensive range and are not responsive to TLCs should receive pharmacologic therapy sufficient to reduce their BP to below the 90th percentile for renal protection benefits. In the absence of obesity, other risk factors, or chronic disease, children and adolescents with prehypertension should have their BP monitored every 6 months along with TLCs.

Stage 1 Hypertension

BP measurement should be repeated to confirm the diagnosis of hypertension within 1 to 2 months. When stage 1 hypertension is verified, a diagnostic evaluation should be performed. It should include an evaluation for comorbidities and target organ damage, as well as identifiable cause. If the evaluation detects an underlying cause of the hypertension, such as renal disease, coarctation of the aorta, or endocrine disorder, further management involves treatment of the underlying cause and controlling the BP. TLCs are appropriate and should be included in the management of stage 1 secondary hypertension, but most patients will also require pharmacologic treatment to control BP to a level that is below the 90th percentile. When no underlying cause for the hypertension is identified and the hypertension is presumed to be primary, initial therapy should focus on TLCs, particularly if the child is obese. Pharmacologic therapy is indicated in stage 1 primary hypertension if the child is symptomatic, has evidence of target organ damage, or has persistent hypertension despite TLCs.

Stage 2 Hypertension

Evaluation should begin in pediatric patients with stage 2 hypertension within a week of diagnosis (sooner if symptomatic). Children, especially the very young, with this degree of hypertension are likely to have secondary hypertension. Some children with stage 2 hypertension may benefit from referral to consultants with expertise in pediatric hypertension. Pediatric patients with stage 2 hypertension will require pharmacologic therapy for BP control, as well as management of the underlying cause if the hypertension is found to be secondary. Some adolescents with stage 2 hypertension may have primary hypertension, particularly if they are also obese. Although drug therapy is required, efforts to achieve weight reduction are also important for obese adolescents with stage 2 hypertension.

ANTIHYPERTENSIVE TREATMENTS FOR CHILDREN AND ADOLESCENTS

Therapeutic Lifestyle Changes

Health-related behavior changes in diet, physical activity, and weight control improve BP control in children, as well as adults. These TLCs are appropriate as a first step in treatment of children and adolescents with stage 1 hypertension who do not have evidence of target organ damage. TLCs may also provide some benefit in preventing a further rise in BP among children with prehypertension.

Obesity is often associated with stage 1 hypertension in childhood, and weight reduction has benefit in obese children. Using a program of both behavior modification and parental involvement, Brownell et al.[52] showed that weight loss in obese adolescents was associated with a significant decrease in BP. Exercise training also lowers BP in school-aged children and adolescents.[53-55] Rocchini et al.[29] showed that a program including both caloric restriction and exercise produced a decrease in BP, as well as a reversal of structural changes in forearm resistance vessels. Weight reduction can be extremely difficult and generally requires multiple strategies that include the input of a nutritionist, dietary education, emotional support, information about exercise, and family involvement.

Increasing physical activity is an important component of TLC. Reversing sedentary behavior should be strongly encouraged through whatever method is most appealing or acceptable to a given child. The methods may include sports participation, exercise plans or workouts, dance classes, or even nonathletic activities. Particularly among girls, there tends to be a decline in leisure-time activity from preadolescence to late adolescence, and the decline in physical activity is associated with greater weight gain and higher body mass index among those who decrease physical activity compared with adolescents who remain physically active.[56] The only form of exercise that should be discouraged in hypertensive adolescents is power weight lifting, due to its potential to induce marked BP elevation during the lifting of excessively heavy weights. Participation in other sports should be encouraged as long as BP is under reasonable control, regular monitoring of BP occurs, and a thorough examination has been conducted to exclude cardiac conditions.[20]

The guidelines for dietary modification in the pediatric population are less clear than in adults. Information on the effects of salt on BP in children is not as definitive as in adults. There does seem to be a subset of adolescents, particularly those who are obese, who demonstrate BP sensitivity to salt, as well as other risk factors for hypertension.[30] Because the usual dietary intake of sodium for most children and adolescents in the United States exceeds nutrient requirements, it is reasonable to restrict sodium intake to less than 4 g/d by decreasing consumption of processed foods and fast-foods and refraining from adding salt to cooked foods.[57]

Data on the effects of potassium and calcium intake on BP in children are even less definitive. The Dietary Approaches to

Stop Hypertension (DASH) trial, which was conducted in adults with stage 1 hypertension or prehypertension, reported results that could be relevant to diet benefits in children. DASH demonstrated a significant reduction in both systolic and diastolic BP in subjects consuming a diet high in fruits, vegetables, and low-fat dairy products compared with the subjects consuming the usual American diet, indicating that a combination of multiple nutrients from diets that are high in potassium, calcium, magnesium, and other vitamins have a beneficial effect on BP.[58] A similar benefit may occur in children, particularly as secular changes in diet patterns and food sources are trending away from the DASH-style diet. Practical recommendations for diet changes in children and adolescents include (1) increase intake of fruits and vegetables to five servings a day; (2) reduce intake of processed foods; and (3) eliminate sugar-containing drinks including sodas and fruit juices.

Pharmacologic Therapy

Pharmacologic therapy is indicated if nonpharmacologic approaches are unsuccessful or when a child is symptomatic, has severe hypertension, or target organ damage. Children with diabetes mellitus or chronic renal disease may achieve renal protective benefits from BP reduction with medication. For children with these disorders it is reasonable to use pharmacologic therapy to lower BP to a level that is below the 90th percentile for age, sex, and height.

Most of the medications used for adults can be used for children. However, efficacy data, as well as long-term safety data, are limited for the pediatric population. The choice of antihypertensive medication should be individualized and depends on the child's age, etiology of the hypertension, degree of BP elevation, adverse effects, and concomitant medical conditions. In most patients therapy is begun with a single agent. The dose is titrated upward until control of the BP is attained. BP control, in most instances, is defined as maintaining systolic and diastolic pressure below the 90th percentile. If control cannot be achieved using the maximum dose of a single agent, a second medication can be added or, alternatively, another agent from a different class selected. The more commonly used medications for chronic antihypertensive therapy in children are listed in Table 40–4 and those for use in acute, hypertensive emergencies in Table 40–5. The dosing recommendations for children are based largely on practitioner experience, not on large, multicenter trials. Some clinical trial work in children is now being conducted using medications that are approved and commonly prescribed for hypertension in adults. This information will provide more information on efficacy, safety, and dosing in children.

β-Adrenergic blockers are good choices in some nonasthmatic children but may not be well tolerated by athletes in whom exercise capacity could be decreased. More frequently, first-line medications are either angiotensin-converting enzyme (ACE) inhibitors or calcium-channel blockers (CCBs). ACE inhibitors rarely cause side effects (e.g., cough, rash, neutropenia) in children and are usually well tolerated. Many formulations have the advantage of once-a-day dosing. They are effective in controlling BP and may have beneficial effects on renal, cardiac, and peripheral vascular (endothelial) function.[59] Importantly, children with diabetes or chronic kidney disease may be at special risk for progressive deterioration of renal function and may benefit from ACE inhibitors.[60,61] Because of their vasodilator effects on the efferent arteriole, ACE inhibitors can severely reduce glomerular filtration and therefore their use should be accompanied by regular monitoring of renal function in patients with renal artery stenosis, a solitary kidney, or a transplanted kidney.[62] ACE inhibitors are contraindicated during pregnancy because of teratogenic effects on the lungs, kidneys, and brain of the fetus.[63] These agents should be used only after thorough discussion of the risks in adolescent girls who may be sexually active. Angiotensin receptor blockers (ARBs) also interact with the renin-angiotensin system and have benefits similar to the ACEs. Some experience is now being developed with these agents in treatment of children with hypertension.

Several of the CCBs are being used in children as initial therapy or as the second or third medication when more than one drug is necessary to control BP. As with most of the oral antihypertensive preparations, the appropriate dose for small children is often lower than the strength of available tablets, which makes initial dose determinations challenging. When CCBs are necessary for BP control in chronic hypertension, long-acting preparations are preferred, provided that the correct dosage preparation can be used.

Diuretics are generally recommended as initial drug therapy for uncomplicated hypertension in adults on the basis of a vast amount of clinical trial data. No such information is available to guide pharmacologic management of hypertension in children and adolescents. Unless there is clinical evidence of fluid retention in a hypertensive child, such as may occur when the elevated BP is related to chronic steroid use, diuretics are usually not the preferred first step in drug treatment. Most hypertensive children will not achieve adequate BP control with a thiazide diuretic alone, and children receiving thiazide diuretics often develop hypokalemia and require potassium supplements. For children, taking potassium supplements is extremely unpleasant, frequently leading to compliance problems. Despite these caveats, a low-dose diuretic can be useful as a second or third drug in children who require multiple drugs to achieve BP control.

SUMMARY

Essential, or primary, hypertension can occur in childhood. Because of the rising rates of childhood obesity, the prevalence of essential hypertension in childhood will increase. Despite this trend, the possibility of secondary hypertension should be considered in all children with documented hypertension. Children with suspected secondary hypertension require a more extensive evaluation than those with apparent essential hypertension. Whether the hypertension is determined to be secondary or primary, these children require monitoring, interventions to control the BP, and long-term follow-up. Considering the long-term morbidity and mortality associated with hypertension, interventions including preventive interventions that focus on BP control beginning in the young are necessary. Essential hypertension encompasses many distinct pathophysiologic entities, each with its own genetic basis and management approach. As new information develops, improved management strategies can be created for hypertension in the young, as well as in adults.

Table 40–4 Antihypertensive Drugs for Outpatient Management of Hypertension in Children 1 to 17 Years Old*

Class	Drug	Dose†	Dosing Interval	Evidence‡	FDA labeling§	Comments¶
Angiotensin-converting enzyme (ACE) inhibitor	Benazepril	Initial: 0.2 mg/kg/d up to 10 mg/d Maximum: 0.6 mg/kg/d up to 40 mg/d	qd	RCT	Yes	1. All ACE inhibitors are contraindicated in pregnancy—females of childbearing age should use reliable contraception. 2. Check serum potassium and creatinine periodically to monitor for hyperkalemia and azotemia. 3. Cough and angioedema are reportedly less common with newer members of this class than with captopril. 4. Benazepril, enalapril, and lisinopril labels contain information on the preparation of a suspension; captopril may also be compounded into a suspension. 5. FDA approval for ACE inhibitors with pediatric labeling is limited to children 6 years of age and older to children with creatinine clearance ≥30 mL/min/1.73 m^2.
	Captopril	Initial: 0.3-0.5 mg/kg/dose Maximum: 6 mg/kg/d	tid	RCT, CS	No	
	Enalapril	Initial: 0.08 mg/kg/d up to 5 mg/d Maximum: 0.6 mg/kg/d up to 40 mg/d	qd-bid	RCT	Yes	
	Fosinopril	Children >50 kg: Initial: 5-10 mg/d Maximum: 40 mg/d	qd	RCT	Yes	
	Lisinopril	Initial: 0.07 mg/kg/d up to 5 mg/d Maximum: 0.6 mg/kg/d up to 40 mg/d	qd	RCT	Yes	
	Quinapril	Initial: 5-10 mg/d Maximum: 80 mg/d	qd	RCT, EO	No	
Angiotensin receptor blocker	Irbesartan	6-12 yr: 75-150 mg/d ≥13 yr: 150-300 mg/d	qd	CS	Yes	1. All ARBs are contraindicated in pregnancy—females of childbearing age should use reliable contraception. 2. Check serum potassium, creatinine periodically to monitor for hyperkalemia and azotemia. 3. Losartan label contains information on the preparation of a suspension. 4. FDA approval for ARBs is limited to children 6 years of age and older and to children with creatinine clearance ≥30 mL/min/1.73 m^2.
	Losartan	Initial: 0.7 mg/kg/d up to 50 mg/d Maximum: 1.4 mg/kg/d up to 100 mg/d	qd	RCT	Yes	
α- and β-Blocker	Labetalol	Initial: 1-3 mg/kg/d Maximum: 10-12 mg/kg/d up to 1200 mg/d	bid	CS, EO	No	1. Asthma and overt heart failure are contraindications. 2. Heart rate is dose limiting. 3. May impair athletic performance. 4. Should not be used in insulin-dependent diabetics.

Table 40–4 Antihypertensive Drugs for Outpatient Management of Hypertension in Children 1 to 17 Years Old*—cont'd

Class	Drug	Dose[†]	Dosing Interval	Evidence[‡]	FDA labeling[§]	Comments[¶]
β-Blocker	Atenolol	Initial: 0.5-1 mg/kg/d Maximum: 2 mg/kg/d up to 100 mg/d	qd-bid	CS	No	1. Noncardioselective agents (propranolol) are contraindicated in asthma and heart failure. 2. Heart rate is dose limiting. 3. May impair athletic performance. 4. Should not be used in insulin-dependent diabetics. 5. A sustained-release formulation of propranolol is available that is dosed once daily.
	Bisoprolol/ HCTZ	Initial: 2.5/6.25 mg/d Maximum: 10/6.25 mg/d	qd	RCT	No	
	Metoprolol	Initial: 1-2 mg/kg/d Maximum: 6 mg/kg/d up to 200 mg/d	bid	CS	No	
	Propranolol	Initial: 1-2 mg/kg/d Maximum: 4 mg/kg/d up to 640 mg/d	bid-tid	RCT, EO	Yes	
Calcium channel blocker	Amlodipine	Children 6-17 yr: 2.5-5 mg once daily	qd	RCT	Yes	1. Amlodipine and isradipine can be compounded into stable extemporaneous suspensions. 2. Felodipine and extended-release nifedipine tablets must be swallowed whole. 3. Isradipine is available in both immediate-release and sustained-release formulations; sustained release form is dosed qd or bid. 4. May cause tachycardia.
	Felodipine	Initial: 2.5 mg/d Maximum: 10 mg/d	qd	RCT, EO	No	
	Isradipine	Initial: 0.15-0.2 mg/kg/d Maximum: 0.8 mg/kg/d up to 20 mg/d	tid-qid	CS, EO	No	
	Extended-release nifedipine	Initial: 0.25-0.5 mg/kg/d Maximum: 3 mg/kg/d up to 120 mg/d	qd-bid	CS, EO	No	
Central α-agonist	Clonidine	Children ≥12 years: Initial: 0.2 mg/day Maximum: 2.4 mg/day	bid	EO	Yes	1. May cause dry mouth and/or sedation. 2. Transdermal preparation also available. 3. Sudden cessation of therapy can lead to severe rebound hypertension.
Diuretic	HCTZ	Initial: 1 mg/kg/d Maximum: 3 mg/kg/d up to 50 mg/d	qd	EO	Yes	1. All patients treated with diuretics should have electrolytes monitored shortly after initiating therapy and periodically thereafter. 2. Useful as add-on therapy in patients being treated with drugs from other drug classes.
	Chlorthalidone	Initial: 0.3 mg/kg/d Maximum: 2 mg/kg/d up to 50 mg/d	qd	EO	No	

Continued

Table 40–4 Antihypertensive Drugs for Outpatient Management of Hypertension in Children 1 to 17 Years Old*—cont'd

Class	Drug	Dose†	Dosing Interval	Evidence‡	FDA labeling§	Comments¶
Diuretic—cont'd	Furosemide	Initial: 0.5-2.0 mg/kg/dose Maximum: 6 mg/kg/d	qd-bid	EO	No	3. Potassium-sparing diuretics (spironolactone, triamterene, amiloride) may cause severe hyperkalemia, especially if given with ACE inhibitor or ARB. 4. Furosemide is labeled only for treatment of edema but may be useful as add-on therapy in children with resistant hypertension, particularly in children with renal disease. 5. Chlorthalidone may precipitate azotemia in patients with renal diseases and should be used with caution in those with severe renal impairment.
	Spironolactone	Initial: 1 mg/kg/d Maximum: 3.3 mg/kg/d up to 100 mg/d	qd-bid	EO	No	
	Triamterene	Initial: 1-2 mg/kg/d Maximum: 3-4 mg/kg/d up to 300 mg/d	bid	EO	No	
	Amiloride	Initial: 0.4-0.625 mg/kg/d Maximum: 20 mg/d	qd	EO	No	
Peripheral α-antagonist	Doxazosin	Initial: 1 mg/d Maximum: 4 mg/d	qd	EO	No	May cause hypotension and syncope, especially after first dose.
	Prazosin	Initial: 0.05-0.1 mg/kg/d Maximum: 0.5 mg/kg/d	tid	EO	No	
	Terazosin	Initial: 1 mg/d Maximum: 20 mg/d	qd	EO	No	
Vasodilator	Hydralazine	Initial: 0.75 mg/kg/d Maximum: 7.5 mg/kg/d up to 200 mg/d	qid	EO	Yes	1. Tachycardia and fluid retention are common side effects. 2. Hydralazine can cause a lupus-like syndrome in slow acetylators. 3. Prolonged use of minoxidil can cause hypertrichosis. 4. Minoxidil is usually reserved for patients with hypertension resistant to multiple drugs.
	Minoxidil	Children younger than 12 yr: Initial: 0.2 mg/kg/d Maximum: 50 mg/d Children ≥12 yr: Initial: 5 mg/d Maximum: 100 mg/d	qd-tid	CS, EO	Yes	

*Includes drugs with prior pediatric experience or recently completed clinical trials.
†The maximum recommended adult dose should not be exceeded in routine clinical practice.
‡Level of evidence upon which dosing recommendations are based (CS, case series; EO, expert opinion; RCT, randomized controlled trial)
§FDA-approved pediatric labeling information is available. Recommended doses for agents with FDA-approved pediatric labels are the doses contained in the approved labels. Even when pediatric labeling information is not available, the FDA-approved label should be consulted for additional safety information.
¶Comments apply to all members of each drug class except where otherwise stated.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; bid, twice-daily; HCTZ, hydrochlorothiazide; qd, once-daily; qid, four times daily; tid, three times daily.

Table 40–5 Antihypertensive Drugs for Management of Severe Hypertension in Children 1 to 17 Years Old

Drug	Class	Dose[†]	Route	Comments
	Most Useful*			
Esmolol	β-blocker	100-500 mcg/kg/min	IV infusion	Very short-acting—constant infusion preferred. May cause profound bradycardia. Produced modest reductions in BP in a pediatric clinical trial.
Hydralazine	Vasodilator	0.2-0.6 mg/kg/dose	IV, IM	Should be given every 4 hr when given IV bolus. Recommended dose is lower than FDA label.
Labetalol	α- and β-blocker	Bolus: 0.2-1.0 mg/kg/dose up to 40 mg/dose infusion: 0.25-3.0 mg/kg/hr	IV bolus or infusion	Asthma and overt heart failure are relative contraindications.
Nicardipine	Calcium channel blocker	1-3 mcg/kg/min	IV infusion	May cause reflex tachycardia.
Sodium nitroprusside	Vasodilator	0.53-10 mcg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 hr) use or in renal failure or coadminister with sodium thiosulfate.
	Occasionally Useful[‡]			
Drug	Class	Dose[†]	Route	Comments
Clonidine	Central α-agonist	0.05-0.1 mg/dose, may be repeated up to 0.8 mg total dose	po	Side effects include dry mouth and sedation.
Enalaprilat	ACE inhibitor	0.05-0.1 mg/kg/dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension and acute renal failure, especially in neonates.
Fenoldopam	Dopamine receptor agonist	0.2-0.8 mcg/kg/min	IV infusion	Produced modest reductions in BP in a pediatric clinical trial in patients up to 12 yr.
Isradipine	Calcium channel blocker	0.05-0.1 mg/kg/dose	po	Stable suspension can be compounded.
Minoxidil	Vasodilator	0.1-0.2 mg/kg/dose	po	Most potent oral vasodilator; long acting.

*Useful for hypertensive emergencies and some hypertensive urgencies.
†All dosing recommendations are based on expert opinion or case series data except as otherwise noted.
‡Useful for hypertensive urgencies and some hypertensive emergencies.
ACE, angiotensin-converting enzyme; IM, intramuscular; IV, intravenous; po, oral.

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Other Cardiovascular Conditions

Chapter 41

Pharmacologic Options for Treating Cardiovascular Disease During Pregnancy

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CHAPTER CONTENTS

Pregnancy leads to an expansion of blood volume and altered pharmacokinetics of therapeutic agents. In addition, cardiovascular therapies may have effects on the fetus by crossing the blood-placenta barrier and on the newborn by excretion in breast milk. Physicians caring for pregnant and lactating patients with cardiovascular disorders should understand the hemodynamic changes associated with pregnancy, as well as the pharmacokinetics of various drugs, in order to make the most rational and safe decisions regarding pharmacologic therapy during pregnancy, delivery, and the early postpartum period.

Increases in human chorionic somatomammotropin lead to an increase in red cell formation and subsequently to an increase in red blood cell mass in pregnancy. High estrogen levels activate the renin-angiotensin axis, which results in sodium and water retention and an increase in extracellular volume. The combined impact of these two changes is to increase blood volume by 30% to 50% over baseline during pregnancy.[1] This increase in blood volume begins before the end of the first trimester and levels off by the middle of the third trimester. Increases in extracellular volume are proportionally larger than increases in red cell volume, one cause of the "anemia of pregnancy."[1] Iron supplementation, which is recommended, can partially correct this "physiologic anemia" of pregnancy.[2]

Cardiac output increases throughout pregnancy by increasing heart rate as well as stroke volume. Multiple factors contribute to a fall in systemic vascular resistance.[2,3,4] The systolic pressure begins to fall during the first trimester, nadirs in midpregnancy, and returns to normal before term. Diastolic pressure decreases more than systolic pressure, thus causing a widened pulse pressure. Decreased blood pressure may be most pronounced during the second trimester and must be considered when prescribing therapies for cardiovascular disorders.

The pharmacokinetics of drugs is altered because of changes in gastrointestinal and renal function during pregnancy. Decreases in gastrointestinal motility are quite heterogenous but may lead to significantly decreased and delayed gastrointestinal absorption. Increases in fatty tissue, as well as decreased maternal hepatic enzyme activity, may decrease the metabolism of some pharmacologic agents. The distribution of the increased cardiac output is altered in pregnancy with a large amount of flow distributed to the uterus to allow fetal growth and development. Renal blood flow increases during pregnancy, with a 30% to 80% increase in glomerular filtration rate. Metabolic considerations for drug dosing in pregnancy are listed in Table 41–1.

The ability of a pharmacologic agent to cross the placental barrier must be considered. Early in pregnancy, the fetal blood-brain barrier is not developed. Therefore agents crossing the placental barrier may affect general fetal development as well as fetal central nervous system development. Data on the safety of pharmacologic agents in pregnancy are paramount, but for many agents clinical data from patients are limited, and recommendations for safety are often

Table 41–1 Factors Leading to Altered Pharmacokinetics in Pregnancy

Altered Systems	Impact of Changes
Gastrointestinal motility	Decreased motility and absorption caused by elevated estrogens
Hepatic enzyme activity	May be decreased in pregnancy, leading to slower metabolism
Increased volume of distribution and increased levels of fatty tissue	Results in altered protein binding and volume of distribution of some agents (e.g., digoxin)
Increased renal blood flow	Increased glomerular filtration rate may lead to increased drug clearance
Altered distribution of cardiac output	Increased proportion of cardiac output dedicated to uterus; impact on fetal-placental unit dependent on ability of agent to cross placental barrier and through fetal tissues

extrapolated from animal data. The text *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* is a useful reference for physicians caring for pregnant patients.[5] Table 41–2 lists the classification of and most common risks associated with the use of cardioactive drugs during pregnancy and lactation.[5]

HYPERTENSION

The treatment of hypertension in pregnancy is covered in Chapter 39.

EDEMA

Peripheral edema is common in pregnancy and may be seen in patients with or without underlying cardiovascular disorders. Routine treatment of edema with diuretics is not recommended. Compression stockings may be useful for women with bothersome edema. These stockings also decrease venous stasis and may be helpful in patients who have a history of venous thromboembolism. Diuretics should be used sparingly in pregnancy because they may interfere with the normal physiologic volume expansion of pregnancy. Loop diuretics are indicated in the management of edema associated with congestive heart failure, nephrosis, cirrhosis, or preeclampsia. Furosemide is generally the diuretic of choice. Furosemide crosses the placenta and may result in increased fetal urine production.[5] Thiazide diuretics cross the placenta and can cause fetal or neonatal jaundice, thrombocytopenia, hypoglycemia, hemolytic anemia, hyponatremia, and fetal bradycardia.[6] Data on the use of potassium-sparing diuretics in pregnancy are inadequate. Spironolactone can adversely affect sexual differentiation in males and is contraindicated in pregnancy.[6] The American Academy of Pediatrics classifies furosemide, thiazides, and spironolactone as compatible with breast-feeding.[5,6]

VALVULAR HEART DISEASE

As the heart enlarges with pregnancy, most women develop a small amount of mitral and tricuspid regurgitation. This amount of regurgitation is only slightly more than physiologic and generally does not produce any symptoms and does not require therapy. Women with preexisting aortic or mitral regurgitation related to structural heart disease tend to tolerate pregnancy well because of the decreased systemic vascular resistance of pregnancy, which serves as a “natural vasodilator.” However, patients with severe aortic or mitral regurgitation may experience difficulty in handling the increased volume load imposed on the heart by pregnancy. In these patients, optimal therapy may include valve repair or replacement before pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are commonly used in nonpregnant patients with severe mitral or aortic regurgitation to decrease the volume load on the left ventricle. Both ACE inhibitors and ARBs cross the placenta and appear to rise to toxic levels in the fetus, mainly affecting the developing urogenital tract but also causing a number of other abnormalities (see Table 41–2). Although limited data suggest that ACE inhibitor exposure in the first trimester may not be harmful,[7,8] without definitive proof of safety early in pregnancy, both ACE inhibitors and ARBs should be avoided throughout pregnancy and discontinued before conception whenever possible. During pregnancy, hydralazine and nitrates can be used as a substitute for ACE inhibitors and ARBs. In symptomatic patients, medical therapies include bed rest, nitrates, digoxin, salt restriction, and loop diuretics. Symptomatic patients may benefit from invasive hemodynamic monitoring during labor and delivery. Epidural anesthesia can be administered safely.[9]

Patients with mild-to-moderate aortic stenosis suffer few cardiovascular complications with pregnancy. However, severe aortic stenosis is poorly tolerated in pregnancy and may lead to increases in medication, hospitalizations, atrial arrhythmias, congestive heart failure, and premature delivery. Fetal outcome is also affected with a higher incidence of preterm birth, intrauterine growth retardation (IUGR), and neonatal respiratory distress syndrome.[10,11] Medical therapy for symptomatic aortic stenosis is limited to diuretics and bedrest. Those patients who are refractory to medical therapy must be treated surgically or with palliative balloon valvuloplasty, a procedure that seems to be associated with a lower risk of fetal loss and is the preferred treatment.[12] Many surgeons have reported successful aortic valve replacement during pregnancy, and surgical valve replacement is associated with a fetal mortality rate up to 30%.[13] During labor, when epidural anesthesia is used, invasive hemodynamic monitoring is recommended to avoid hypotension and reflex tachycardia during labor and delivery. Vaginal delivery is preferred with assisted second stage of labor. General anesthesia is the preferred technique for cesarean section.[14] Postpartum hemorrhage can be catastrophic for women with severe aortic stenosis and must be managed aggressively.

Patients with rheumatic mitral stenosis may first develop symptoms during pregnancy. As heart rate and cardiac output

Table 41–2 Risk of Cardiac Drugs to Fetus and Newborn—cont'd

Drug	Placental Transfer	Risk Factor*	Fetal Effects	Breast-Feeding Risk
Mexiletine	Yes	C_M	No adverse effects reported	Limited data—probably compatible; excreted into milk
Nesiritide	Unknown	C	No data	No data
Nifedipine	Yes	C_M	No teratogenic effect reported; important interaction with IV magnesium	Limited data—probably compatible
Nitroglycerin	Unknown	B/C_M	No adequate human studies	No data—probably compatible
Procainamide	Yes	C_M	None	Limited data—probably compatible
Propafenone	Unknown	C_M	No adequate human data	No data—probably compatible
Propranolol	Yes	C_M	Growth retardation, prematurity, hypoglycemia, bradycardia, respiratory depression	Limited data—potential toxicity
Quinidine	Yes	C_M	Thrombocytopenia	Limited data—probably compatible
Sodium nitroprusside	Yes	C	Potentially toxic; no adequate human studies	No data; potential toxicity
Sotalol	Yes	B_M/D if used in 2nd or 3rd trimester	Bradycardia; used to treat fetal tachycardia; IUGR, decreased placental weight	Limited data—potential toxicity
Spironolactone	Unknown	C_M/D if used in gestational hypertension	No human congenital defects reported; known antiadrogenic effects	Limited data—probably compatible
Streptokinase	Yes (minimal)	C_M	No reports of congenital anomalies	No data—probably compatible
tPA	Probably not	C_M	No teratogenicity observed	Compatible
Unfractionated heparin	No	C_M	Thrombocytopenia, acute distress	Yes
Verapamil	Yes	C_M	No reports of congenital anomalies	Limited data—probably compatible
Warfarin	Yes	D_M/X according to manufacturer DuPont Pharma, 2000	Abortion, hemorrhage, nasal hypoplasia, stippled epiphyses	Compatible

*Risk factors: Category B: Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters). Category C: Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in pregnant women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is necessary for a life-threatening situation for which safer drugs cannot be used or are ineffective). The M subscript indicates that the manufacturer has rated the risk. X denotes that the manufacturer designates the drug as contraindicated in pregnancy.
Data mainly from Briggs GG, Freeman RK, Yaffe SJ: Drugs in Pregnancy and Lactation, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2005.

increase during the second trimester, the diastolic filling period decreases and left atrial pressure increases. These changes may lead to atrial distention, which may be associated with dyspnea and the development of atrial fibrillation. Left atrial filling pressures may be reduced by the use of loop diuretics and β-adrenergic blocking agents. β-Blockers decrease heart rate and increase the diastolic filling period. Use of β-1-selective agents is preferred due to the lack of interference with β-2-mediated uterine relaxation.[15] Restriction of physical activity is also important in controlling heart rate and symptoms. Atrial fibrillation may be poorly tolerated during pregnancy and, in a hemodynamically unstable patient, should be promptly treated with cardioversion. Rapid restoration of sinus rhythm decreases left atrial pressure and congestive symptoms. However, the risk of thromboembolic complications must be considered before cardioversion. To rule out the presence of left atrial thrombus, transesophageal echocardiography (TEE) should be performed before cardioversion. Full-dose anticoagulation is indicated for pregnant patients with mitral stenosis and atrial fibrillation.

Pregnancy is a hypercoagulable state due to the increased levels of factors I, II, VII, VIII, IX, and X and may increase the

risk of thromboembolism in patients with severe mitral stenosis even in the absence of atrial fibrillation. Left atrial thrombus has been reported in three pregnant women with mitral stenosis in sinus rhythm.[16] The first patient suffered a left middle cerebral artery stroke, a second had partial occlusion of the mitral valve orifice, and the third patient had worsening of heart failure.[14,16]

For patients presenting with atrial fibrillation, digoxin and β-blockers can be used safely to control the ventricular response. If a third drug is necessary to control ventricular rates, a calcium channel blocker can be added. Verapamil is not teratogenic and appears relatively safe, although maternal hypotension has been reported after intravenous bolus of verapamil.[5] When used to treat fetal supraventricular arrhythmias, verapamil can cause fetal bradycardia, heart block, depression of contractility, hypotension, and fetal demise.[17] There is less experience with diltiazem during pregnancy, but short-term use of intravenous diltiazem to control ventricular rate may be considered safe and effective. A Michigan Medicaid surveillance study suggests an association between use of diltiazem during pregnancy and congenital cardiovascular defects.[5]

Patients who have symptoms related to mitral stenosis before the end of the first trimester (which is the beginning of volume expansion for these patients) are unlikely to tolerate pregnancy well. Percutaneous valvuloplasty or surgical commissurotomy should be considered for these patients. Percutaneous balloon mitral valvuloplasty during pregnancy has been reported in numerous patients with good outcomes.[9,14] The procedure should be avoided in the first trimester to avoid fetal radiation during organogenesis and should be reserved for those who are refractory to medical therapy. Mitral valve surgery should be considered only for medically refractory patients who are not suitable candidates for percutaneous valvuloplasty because the risks to mother and fetus are significantly greater. With surgery, the maternal mortality rate has been reported as 9% and the fetal or neonatal mortality rate as 29%.[12] Vaginal delivery with assisted second stage of labor can be permitted, with cesarean section reserved for obstetric indications. Invasive hemodynamic monitoring is recommended with use of epidural anesthesia.[18] β-Blocking agents (and occasionally diuretics) may be used to decrease the left atrial filling pressures at the time of delivery. The autotransfusion of blood from the uterus shortly after delivery is associated with an increase in left atrial filling pressures (increases of ≈ 10 mm Hg might be expected) and can precipitate pulmonary edema.

Isolated valvular pulmonic stenosis (PS), even when severe, is typically well tolerated throughout pregnancy. Although the number of reported pregnancies complicated by isolated PS is small, severe PS does not seem to adversely affect maternal or fetal outcome. Balloon valvuloplasty should be considered in symptomatic patients. Pulmonic stenosis is frequently associated with more complex congenital heart disease, which is reviewed in Chapter 42.

THROMBOEMBOLIC DISEASE DURING PREGNANCY

Anticoagulation is indicated during pregnancy for the prevention and treatment of venous thromboembolism, for patients with mechanical heart valves, and for the prevention of complications in women with thrombophilia or recurrent late pregnancy loss. Pregnancy is a hypercoagulable state because of the increased production of clotting factors, an acquired resistance to the endogenous anticoagulant, activated protein C, and a decrease in fibrinolysis.[19] This prothrombotic state, along with lower-extremity venous stasis caused by an enlarging uterus, increases the likelihood of deep venous thrombosis during pregnancy. Venous thromboembolism is 5 to 6 times more common in pregnant women as compared with nonpregnant women, and pulmonary embolism remains a leading cause of maternal mortality throughout the United States.

Acquired or hereditary thrombophilias occur in almost two thirds of women who present with recurrent miscarriages, preeclampsia, IUGR, abruptio placentae, or stillbirths that are associated with microvascular thrombosis in placental blood vessels.[19,20] Because thrombophilic disorders can be seen in up to 20% of normal pregnancies, screening for thrombophilia is recommended only for selected women with unexplained late or recurrent fetal losses of unclear etiology. Anticoagulation strategies are controversial. In general, thromboembolic prophylaxis is recommended for those individuals who are at increased risk and therapeutic anticoagulation is recommended for those individuals who are at highest risk. The Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotics and Thrombolytic Therapy provides evidence-based guidelines on the use of antithrombotic agents during pregnancy.[20a]

ANTICOAGULATION DURING PREGNANCY

The antithrombotics currently available for the prevention and treatment of thromboembolism and valve thrombosis include unfractionated heparin (UFH), low molecular weight heparin (LMWH), heparinoids, coumarin derivatives, and aspirin. The direct thrombin inhibitors, such as hirudin, cross the placenta and have not been evaluated during pregnancy. In evaluating an anticoagulant strategy, there are two potential fetal complications of treatment to consider: teratogenicity and bleeding. Neither UFH, LMWH, nor heparinoids cross the placenta and therefore do not have the potential to cause fetal bleeding or teratogenicity. Numerous studies have shown that UFH and LMWH therapy are safe for the fetus. In contrast, coumarin derivatives cross the placenta and have the potential for fetal bleeding and teratogenicity. Coumarin's effect on the fetus is most marked during the first trimester. The fetal warfarin embryopathy consists of nasal hypoplasia, which can result in nasal bridge depression, upper airway obstruction, and stippled epiphyses.[21] Significant central nervous system abnormalities including microcephaly, optic atrophy, and hydrocephalus have been reported, as well as spontaneous abortions, stillbirths, and neonatal deaths.[21] The exposure period of greatest risk for warfarin embryopathy and spontaneous abortion is between the 6th and 12th weeks of gestation. However, the period of risk for the developing CNS abnormalities is controversial and may extend throughout pregnancy. One cohort study reported a higher incidence of neurodevelopmental problems in children who were exposed to coumarin in the second and third trimesters.[22] Ongoing

exposure to coumarin may result in cerebral microhemorrhages and abnormal brain development.

In a systematic review of the literature on anticoagulation management during pregnancy in women with mechanical heart valves, Chan reported the risk of warfarin embryopathy to be 6.4% in 1234 pregnancies.[23] When warfarin was discontinued and heparin was used prior to 6 weeks' gestation and continued through 12 weeks, the risk of warfarin embryopathy was eliminated entirely. Warfarin use throughout pregnancy was associated with the lowest risk of valve thrombosis, 3.9%, which increased to 9.2% with substitution of heparin from weeks 6 to 12. Warfarin use between 6 and 12 weeks' gestation was associated with a 33.9% spontaneous abortion rate, compared with a rate of 14.7% when heparin was used before week 6. It is noteworthy that 46% of the patients had first-generation valves, typically cage and ball valves or Bjork-Shiley single-tilting disk valves, with only 7.1% having newer bileaflet valves. Chan concludes that use of heparin in the first trimester eliminates the fetal warfarin embryopathy and lowers the spontaneous abortion rate but subjects the woman to an increased risk of valve thrombosis/thromboembolism.

In clinical practice, the use of warfarin during pregnancy varies. Most clinicians avoid warfarin entirely throughout pregnancy. Other clinicians reintroduce warfarin after the first trimester and discontinue its use at approximately 36 weeks, to avoid major maternal and fetal bleeding during late pregnancy and around the time of delivery. If the mother is fully anticoagulated with warfarin at the onset of labor, fresh-frozen plasma should be administered. Warfarin can usually be restarted on the first postpartum day. Overlap therapy with intravenous UFH may be necessary until warfarin becomes effective, depending on the maternal indication for anticoagulation. Warfarin is safe to administer to women who are breast-feeding and does not alter clotting mechanisms in the infant.[24]

UFH has been used extensively for treating thrombotic disorders associated with pregnancy. Potential complications of its use include hemorrhage, thrombocytopenia, and osteopenia. Significant osteopenia may occur in up to one third of women treated with long-term UFH.[25] Thrombocytopenia is a less common adverse effect, but it may affect up to 10% of patients. Approximately 3% of nonpregnant patients treated with UFH acquire immune, IgG-mediated thrombocytopenia, which is frequently complicated by extension of preexisting venous thromboembolism or new arterial thrombosis.[26] This represents a serious complication of heparin therapy and necessitates monitoring the platelet count throughout the course of treatment. Long-term heparin therapy during pregnancy is feasible via subcutaneous injection or continuous intravenous infusion. Dosing of UFH requires adjustment throughout pregnancy. Subcutaneous UFH may have to be administered at doses as high as 10,000 to 20,000 U every 8 to 12 hours in order to maintain midinterval activated partial thromboplastin time (aPTT) of 2 to 3 times control or an anti-Xa level 0.35 to 0.70 IU/mL. Monitoring of a predose (trough) level is useful in determining the need for every-8-hour dosing.[27] For patients in whom subcutaneous UFH therapy is ineffective, continuous infusion of UFH may be used. Placement of a semipermanent indwelling line makes this feasible.[28] Small infusion pumps are available and may be loaded with prefilled heparin cartridges. Subcutaneous UFH should be discontinued 24 hours before elective induction of labor, whereas intravenous UFH should be discontinued 4 to 6 hours before the expected time of delivery.[29]

For many physicians, LMWH has become the preferred agent for the prevention and treatment of venous thromboembolism during pregnancy and for the management of pregnant women with mechanical heart valves. LMWHs have approximately 92% bioavailability compared with 30% of UFH, and they have a longer half-life (4 hours) compared with UFH (3 hours when administered subcutaneously). Moreover, LMWHs have a more predictable anticoagulant response and a lower incidence of heparin-induced thrombocytopenia (HIT), osteopenia, and bleeding complications. Increasing experience has been reported regarding the use of LMWH in pregnancy.[30-34] In one review of 486 pregnancies in which LMWH was administered, symptomatic osteoporosis was observed in only 1 patient, and only 3 patients suffered a thromboembolic event.[34] Allergic reactions and minor bleeding were rare, reported in 2.7%. LMWHs are frequently administered twice daily in high-risk patients. Enoxaparin is most commonly administered subcutaneously at 1 mg/kg twice a day. The dose of enoxaparin may have to be adjusted during pregnancy as maternal weight and drug clearance increases. Dalteparin can be dosed 100 IU/kg every 12 hours. Many have advocated the use of peak or trough anti-Xa levels, or both, to assess adequacy of anticoagulation.[27,29]

Pregnancy in a patient with a mechanical heart valve poses difficult issues with respect to anticoagulation. Pregnant women with prosthetic heart valves are at particularly high risk for thromboembolic complications, with incidence ranging from 7.5% to 23%.[27,35,36] Most events present as valve thrombosis, with an associated mortality rate of 40%.[35-37] The highest-risk patients are those with older, higher-profile mechanical mitral valves, such as the Bjork-Shiley or Starr-Edwards caged ball valve, those in atrial fibrillation, and those with left ventricular dysfunction.[23,27]

There are several case reports and small series on the use of LMWH in pregnant women with prosthetic heart valves, some of which have described treatment failures. Further review has shown that many of the complications were associated with an inadequate dose, lack of monitoring, or subtherapeutic anti-Xa levels.[27] A randomized, open-label trial was designed to compare enoxaparin with warfarin in pregnant women with prosthetic valves. The trial was terminated after enrollment of only 12 patients due to 2 deaths from prosthetic valve thrombosis in the enoxaparin group. Both deaths occurred in high-risk patients who had subtherapeutic anti-Xa levels (less than the recommended 0.3 to 1.0 IU/mL). It is unclear whether the outcomes would have been different with coumarin, and many experts believe the trial should not have been terminated.[38]

For pregnant women with prosthetic heart valves, the ACC/AHA Task Force report in 1998[39] recommended the use of warfarin, especially in high-risk women, through week 35. The Task Force recommended a target INR 2.0 to 3.0 along with administration of low-dose aspirin.[6,39,40] Guidelines from the ACCP outline three possible regimens for women with mechanical heart valves: (1) use of either LMWH or UFH between 6 and 12 weeks and close to term only, with use of vitamin K antagonists (VKAs) at other times; (2) aggressive dose-adjusted UFH throughout pregnancy; or (3) aggressive

Table 41–3 Recommended Approach for Anticoagulation Prophylaxis in Women with PHV During Pregnancy

Higher Risk	Lower Risk
First-generation PHV (e.g., Starr-Edwards, Bjork Shiley) in the mitral position, atrial fibrillation, history of TE on anticoagulation	Second-generation PHV (e.g., St. Jude Medical, Medtronic-Hall) and any mechanical PHV in the aortic position
Warfarin (INR 2.5 to 3.5) for 35 wk, followed by UFH (midinterval aPTT > 2.5) or LMWH (predose anti-Xa ≈0.7) + ASA 80-100 mg q.d. OR UFH (aPTT 2.5 to 3.5) or LMWH (predose anti-Xa ≈0.7) for 12 wk, followed by warfarin (INR 2.5 to 3.5) to 35th week, then UFH (aPTT > 2.5) or LMWH (predose anti-Xa ≈0.7) + ASA 80-100 mg q.d.	SC UFH (midinterval aPTT 2.0 to 3.0) or LMWH (predose anti-Xa ≈0.6) for 12 wk, followed by warfarin (INR 2.5 to 3.0) for 35 wk, then SC UFH (midinterval aPTT 2.0 to 3.0) or LMWH (predose anti-Xa level ≈0.6) OR SC UFH (midinterval aPTT 2.0 to 3.0) or LMWH (predose anti-Xa ≈0.6) throughout pregnancy

aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; INR, international normalized ratio; LMWH, low molecular weight heparin; PHV, prosthetic heart valve; SC subcutaneous; TE, thromboembolism; UFH, unfractionated heparin.
From Elkayam U, Singh H, Irani A, et al: Anticoagulation in pregnant women with prosthetic heart valves. J Cardiovasc Pharmacol Ther 2004;9:107-15.

adjusted-dose LMWH throughout pregnancy.[29] With use of coumarin, the recommended INR is 3.0 with a range of 2.5 to 3.5 or a range of 2.0 to 3.0 if the patient has a bileaflet aortic valve and does **not** have atrial fibrillation or LV dysfunction. UFH should be initiated at high doses and adjusted to maintain aPTT at least 2x control or anti-Xa level 0.35 to 0.70 U/mL. LMWH should be given every 12 hours in doses adjusted to maintain a 4-hour postinjection anti-Xa level 1.0 to 1.2 U/mL or, suboptimally, according to weight. In a review of the management of prosthetic valves in pregnancy, Elkayam[27,41] and Bitar modified the recommendations of the ACC/AHA and the Seventh ACCP Consensus by differentiating between patients at higher and lower risk and by advocating use of both peak and trough levels of heparin activity (Table 41–3). Peak levels should be checked to prevent toxicity and should be less than 1.5, ideally 1.0 to 1.2. Biweekly monitoring of the aPTT or anti-Xa levels is recommended. Higher-risk patients include those with first-generation mechanical mitral valves, a history of atrial fibrillation, previous thromboembolism, or significant left ventricular dysfunction. Thromboembolic prophylaxis in higher-risk patients seems best achieved with coumarin during the first 35 weeks. A higher level of anticoagulation is recommended with target INR 2.5 to 3.5, aPTT >2.5, or predose anti-Xa level approximately 0.7. For higher-risk patients who want to avoid coumarin during the first trimester, UFH or LMWH can be used from weeks 0 to 12 and then again after 35 weeks. All of the contemporary guidelines recommend adding low-dose aspirin (80 to 100 mg) for high-risk patients because it has been shown to decrease the incidence of valve thrombosis in nonpregnant patients, albeit with a slight increase in bleeding risk.[42,43] For the lower-risk group, Elkayam and Bitar[2,27,41] recommend a lower level of anticoagulation: INR 2.5 to 3.0, aPTT 2.0 to 3.0, or predose anti-Xa level of approximately 0.6 (see Table 41–3).

THROMBOLYSIS

Although pregnancy has been perceived as an absolute contraindication to fibrinolysis, fibrinolytic agents have been used in pregnant patients for a variety of indications including iliac vein thrombosis, acute myocardial infarction, massive pulmonary embolism, stroke, renal vein thrombosis, and prosthetic valve thrombosis.[27,44-47] Fibrinolytic agents, such as streptokinase and tissue plasminogen activator, have been used in pregnancy for ST-elevation myocardial infarction (STEMI) and pulmonary embolism that is complicated by hemodynamic instability or right ventricular dysfunction.[48-50] These agents have been used during the first trimester without overt developmental abnormalities. No congenital defects are known to be associated with the use of fibrinolytic agents. The risks of these agents include significant bleeding, peripheral embolization, premature labor, and death. A few cases of placental abruption and neonatal intracranial hemorrhage have been reported.[51] Depending on the case, however, the benefits may outweigh the risks. Streptokinase does cross the placenta in small amounts but has minimal fibrinolytic effects; streptokinase antibodies do cross the placenta.

ISCHEMIC HEART DISEASE

Unstable angina and acute myocardial infarction (MI) may develop in pregnancy through a variety of mechanisms including spontaneous coronary artery dissection; atherosclerotic coronary artery disease (CAD); or use of a toxin, such as cocaine. Women who present with symptomatic CAD in pregnancy tend to be patients with a high burden of cardiovascular risk (i.e., diabetes, smoking, hypertension, lipid disorders, or family history of premature CAD). Mortality rates from MI appear to be higher in late pregnancy and may be attributable to the increased hemodynamic demands on the heart during

this period. Optimal delivery in the peri-infarct period requires coordination and planning by the cardiologist, obstetrician, pediatrician, and anesthesiologist.[52,53]

In general, treatment of STEMI during pregnancy is unchanged from that of the nonpregnant patient. Both fibrinolytic therapy and percutaneous coronary intervention (PCI) have been used in pregnant patients with acute coronary syndromes.[49,50,54,55] In STEMI, primary PCI may be preferred over fibrinolysis because it may reveal a nonatheromatous etiology of coronary insufficiency and carries a lower bleeding risk. Although concerns about PCI have focused on the risks of contrast agents and radiation to the fetus, radiation shielding can be performed to decrease the radiation exposure. Expected exposure rates for PCI range from less than 0.01 to 0.1 Gy, depending on the complexity of the procedure.[51] Isolated case reports document successful use of antiplatelet agents, such as clopidogrel and platelet GP IIb/IIIa inhibitors in pregnancy.[55] However, these agents should be used only with the understanding that there is an increased risk of maternal and fetal bleeding. The safety of drug-eluting stents in pregnant subjects is unknown. Moreover, the duration and safety of poststent antiplatelet therapy has not been studied. Coronary artery bypass during pregnancy carries high risk to the fetus (estimated death rate 19%), whereas the maternal risk is similar to that in nonpregnant patients.[56]

Antianginal therapy during pregnancy includes β-adrenergic blocking agents, calcium channel blocking agents, heparin, and nitrates.[5,57,58] The risks of β-adrenergic blocking agents have been described previously (see Table 41–2). Reports on the use of nitroglycerin during pregnancy, especially during the first trimester, are limited. Transdermal nitroglycerin patches have been used as tocolytic agents. Hypotension and headaches are common side effects of nitrate use, as they are in nonpregnant individuals (see Chapter 5).

In nonpregnant patients, diltiazem has been used successfully to treat ischemia. As previously reviewed, there are limited human data on the use of diltiazem in pregnancy and verapamil is the preferred calcium channel blocker. Nifedipine has been used successfully for the treatment of severe hypertension in pregnancy; however, severe adverse reactions have been reported when the drug is combined with intravenous magnesium. No reports on the use of amlodipine in human pregnancy or lactation are available.

Previous recommendations suggested avoiding aspirin during pregnancy due to the potential risk of premature closure of the ductus arterious. However, a meta-analysis and a large randomized trial found no increased risk of fetal or maternal side effects with aspirin doses of 60 to 150 mg daily.[29,59] High doses of aspirin (325 to 650 mg daily) should be avoided throughout pregnancy. The drug may affect maternal and fetal hemostasis and may cause cardiovascular septal defects, IUGR, and premature ductal closure, which may lead to persistent pulmonary hypertension of the neonate.[5] We recommend using low-dose aspirin (81 to 162 mg daily) throughout pregnancy and lactation in patients with known CAD. Aspirin is excreted into breast milk in low concentrations, but no adverse effects on platelet function in the nursing infant exposed to aspirin have been reported.[5,6] The American Academy of Pediatrics advises cautious use of aspirin during lactation.[5]

LIPID DISORDERS

Few data are available on the use of statins during pregnancy.[60-62] Some animal data demonstrate developmental abnormalities with high-dose fluvastatin and atorvastatin.[6] Postmarketing surveillance reports of exposure to lovastatin and simvastatin during pregnancy are available and include 134 patients with variable exposure to these agents.[6,60,62] Pregnancy outcomes were not markedly different from those of a normal population; however, the number of patients was adequate only to exclude a threefold to fourfold increase in adverse outcomes. Because the risks of statin drugs during pregnancy are unclear and the benefits of treatment of these disorders during pregnancy are unknown, the current recommendation is to stop statin drugs before conception and avoid them throughout pregnancy and lactation.

Although there are limited data on fetal effects from bile acid sequestrants, such as cholestyramine and colestipol, these drugs are not absorbed and therefore should not be teratogenic. A theoretical risk to the fetus from the reduced maternal absorption of fat-soluble vitamins exists. Given the lack of data, these drugs should be avoided throughout pregnancy. No reports of bile acid sequestrant use in lactation have occurred, but the drugs are considered compatible with breast-feeding.[5] Little information is available on the use of nicotinic acid, gemfibrozil, fenofibrate, or ezetimibe in human pregnancy. Animal studies with high-dose gemfibrozil, fenofibrate, and ezetimibe demonstrate toxic fetal effects.[5]

In general, discontinuation of lipid-lowering drugs is likely to expose the mother to minimal risk. Given the lack of data on fetal effects, cholesterol-lowering drugs should be discontinued before conception and avoided throughout pregnancy and lactation.

HEART FAILURE

Peripartum cardiomyopathy (PPCM) is defined as the development of dilated cardiomyopathy (DCM) from the last month of pregnancy through the first 6 months after delivery, when other causes of heart failure have been excluded.[2] This diagnosis is associated with mortality rates ranging from 9% to 50%, depending on the series.[2,9,63-65] The outcome for PPCM appears to be better than that for idiopathic DCM, with approximately 50% of patients with PPCM demonstrating marked improvement in ventricular function and clinical symptoms compared with 10% in idiopathic DCM.[65]

Treatment of PPCM is similar to that for congestive heart failure of any etiology: preload reduction with sodium and fluid restriction, diuretics and nitrates; afterload reduction; and positive inotropes, such as digoxin. Digoxin is relatively safe for both the fetus and the mother and may be used safely while the mother is breast-feeding.[66,67] Diuretics should be used sparingly to avoid a decrease in placental perfusion. Furosemide is the diuretic of choice. Spironolactone should be avoided. No data are available on the use of eplerenone.

Afterload reduction is advantageous for many patients with heart failure. ACE inhibitors and ARBs should be avoided until after delivery because they are teratogenic. Hydralazine, with or without concomitant use of nitrates, is another treatment option for vasodilation during pregnancy. There is

extensive experience with hydralazine in pregnancy, with no significant adverse maternal or fetal outcomes seen.[68] Use of hydralazine is associated with a higher incidence of development of a lupus-like syndrome in the mother. Although it is excreted in breast milk in low concentrations, hydralazine may be used by the nursing mother. Addition of β-blockers can be considered, especially in the setting of arrhythmia. However, because the use of β-blockers is associated with low birth weight and the benefit of β-blockers in heart failure is a long-term benefit, it is prudent to initiate β-blockade after delivery. No human data on the use of carvedilol or nesiritide in pregnancy are available. Therefore, use of these drugs is best reserved for postpartum medical management.

Patients with PPCM have a high rate of thromboembolism, which may complicate up to 53% of cases.[69] Full-dose anticoagulation is recommended for PPCM patients with ejection fraction less than 35%.[65,70] Because the diagnosis of PPCM is made in the last month of pregnancy, LMWH or UFH is preferred over warfarin. Warfarin can be initiated postpartum.

For the hemodynamically unstable patient with heart failure, the first priority is reestablishing adequate maternal circulation with inotropic or mechanical support as needed. If cardiac output is inadequate to support the fetus or if the supportive therapy for the mother puts the fetus at risk, prompt delivery is recommended. Following delivery, the medical regimen should be altered to include β-blockers and ACE inhibitors, as tolerated. Cardiac transplantation has been performed successfully in the postpartum period.

Subsequent pregnancies in patients with PPCM are associated with adverse outcomes. Elkayam et al.[71] reviewed the outcomes of 60 subsequent pregnancies in 44 women with PPCM. In 16 patients with left ventricular dysfunction before subsequent pregnancy, 44% developed symptoms of heart failure compared with 21% of the 28 patients with normal left ventricular function before the pregnancy. Three deaths (19%) were reported in the group with prepregnancy left ventricular dysfunction. Because of the high rate of maternal morbidity and mortality rates associated with subsequent pregnancy, women with PPCM should consult with a cardiologist before conception. A baseline echocardiogram is recommended, along with follow-up for signs and symptoms of heart failure.

CARDIAC ARRHYTHMIAS

The evaluation of a pregnant woman with an arrhythmia should include assessment of cardiac structure and function; pulmonary status; hematocrit; thyroid function; and extrinsic precipitants, such as caffeine, sympathomimetic amines, and alcohol. An echocardiogram is indicated to rule out congenital defects, ventricular dysfunction, and valvular disease. A diagnosis of inappropriate sinus tachycardia is made in a patient with sinus tachycardia out of proportion to the stage of pregnancy in the absence of thyroid disease, anemia, cardiac dysfunction, extrinsic precipitants, or infection. Inappropriate sinus tachycardia may be associated with maternal anxiety and high sympathetic tone. These patients may experience dyspnea at low workloads. Appropriate volume and salt expansion may limit the symptoms produced by this disorder. Treatment with β-adrenergic blocking agents is effective for this disorder but should be prescribed only for severe cases, given the relatively benign nature of this condition and the potential harmful effects of β-blockers on fetal growth.

With the normal volume expansion of pregnancy, atrial expansion may lead to increased atrial irritability and precipitate atrial fibrillation or supraventricular tachycardia (SVT). Atrial premature contractions may be associated with symptoms but rarely need to be treated in pregnancy. For patients with SVT, vagal maneuvers should be attempted first. If vagal maneuvers are not effective, intravenous adenosine is highly effective for the termination of such arrhythmias.[72-74] Adenosine has a short half-life, making it a safe drug for use in pregnancy. No fetal complications related to adenosine have been reported. β-Adrenergic blocking agents and verapamil have been used successfully to terminate supraventricular arrhythmias.[17,75]

Recurrent episodes of SVT may warrant suppressive antiarrhythmic therapy. In the absence of preexcitation, atrioventricular nodal blocking agents may be used. Extensive use of digoxin in pregnancy has occurred without reported significant side effects. The volume of distribution of digoxin is increased during pregnancy, which may lead to an increased dosage requirement (0.25 to 0.50 mg daily). β-blocking agents and verapamil have been used to suppress SVT.

Atrial fibrillation and atrial flutter may develop in pregnancy. For patients with significant structural heart disease, development of atrial fibrillation or flutter can result in acute hemodynamic decompensation and urgent cardioversion may be required. For patients who need antiarrhythmic therapy to assist conversion, quinidine is a good choice because it has been used in pregnancy for more than 50 years. Quinidine toxicity in the mother can lead to severe nausea, vomiting, diarrhea, light-headedness, and tinnitus. Cardiac effects include hypotension, torsades de pointes, and sudden death. Quinidine crosses the placenta, leading to similar fetal and maternal serum levels. Although neonatal thrombocytopenia has been reported, this agent is classified as relatively safe in pregnancy.[6,76,77] Quinidine also has oxytocic properties at high doses but rarely results in pregnancy loss. It is excreted in breast milk but does not cause major problems for the nursing infant.

Procainamide has also been used for the treatment of atrial and ventricular arrhythmias and is not associated with any developmental abnormalities.[76] Procainamide and its primary metabolite, *N*-acetylprocainamide, are excreted in breast milk but are not associated with adverse short-term effects.[78] Little is known about the long-term impact of this agent on the development of antinuclear antibodies or lupus-like syndromes in the child.

Flecainide and propafenone, both class IC agents, are useful in managing ventricular and supraventricular tachycardias and appear to be relatively safe during pregnancy.[5,17,79] There is more experience with flecainide than with propafenone because it has been used successfully in the treatment of fetal tachycardias. All IC agents should be avoided in patients with prior myocardial infarction or cardiomyopathy due to the increased risk of mortality, as reported in the CAST trial.[80]

Sotalol is a class III agent with noncardiac selective β-receptor antagonist properties and is generally considered safe. Sotalol has become a first- or second-line agent in the treatment of fetal tachycardia.[79] Of greatest concern with

sotalol is the proarrhythmic risk in both the mother and the fetus. Ibutilide and dofetilide are class III antiarrhythmics, which have been released for the acute conversion of atrial flutter and fibrillation in nonpregnant patients. There are no reports of their use in pregnancy, and they should be avoided. Amiodarone is widely used in the conversion of atrial fibrillation/flutter, maintenance of sinus rhythm, and in the treatment of ventricular tachycardia. Amiodarone, however, contains iodine and leads to increased circulating iodine levels.[81] The elevated iodine levels may produce neonatal hypothyroidism. Use of amiodarone in pregnancy is restricted to severe or life-threatening arrhythmias that cannot be effectively treated with other agents.

Although many women experience an increase in ventricular premature beats during pregnancy, few develop nonsustained or sustained ventricular tachycardia. Ventricular tachycardia in patients without structural heart disease generally carries a low risk for mortality and morbidity and can often be treated with β-blocking agents. Patients with long QT syndrome, ischemic heart disease, or cardiomyopathies who have ventricular tachycardia are at higher risk for serious arrhythmias. For hemodynamically tolerated ventricular tachycardia, treatment should begin with lidocaine or procainamide. Lidocaine crosses the placenta and readily appears in the fetal circulation. It has been associated with central nervous system depression in the newborn if high levels are achieved. Nonetheless, it remains appropriate therapy for acute treatment of ventricular tachycardia. Type IC agents, such as flecainide and propafenone, are contraindicated for patients with structural heart disease. Some of these patients may have to be treated with chronic suppressive antiarrhythmic therapy or with implantable devices, depending on the nature of their underlying disorder. Minimal fetal radiation exposure should be required for successful placement of a device during pregnancy.

Cardiopulmonary resuscitation is rarely necessary during pregnancy.[82] Effective delivery of chest compressions may be difficult, and positioning the patient on her left side may optimize blood return from the periphery. If the arrest occurs before fetal viability, efforts should be directed toward maternal resuscitation. If the arrest occurs after this time, the focus of the resuscitation is on both the mother and the fetus, which should be delivered rapidly by cesarean section.

MARFAN'S SYNDROME

The most common cardiovascular manifestations of Marfan's syndrome include myxomatous mitral valve disease with mitral regurgitation, aortic regurgitation, aortic root enlargement, and aortic dissection. Patients with Marfan's syndrome are at increased risk for aortic dissection during pregnancy.[83] Patients at highest risk for this complication are those with significant aortic root enlargement (>4.0 cm) before pregnancy.[83] Even patients without significant aortic root dilatation before pregnancy are at a higher risk for this complication than are patients without Marfan's syndrome.

The use of β-blockers is associated with a decreased rate of aortic root dilatation and a decrease in the progression of aortic regurgitation. These agents also attenuate the risk of aortic dissection during pregnancy. For these reasons, patients with Marfan's syndrome should be treated with a β-blocker throughout pregnancy. Preconception counseling is crucial to examine maternal risk and optimize the medical therapy for women at acceptable risk for pregnancy.

PULMONARY HYPERTENSION

Women with significant pulmonary hypertension are at extremely high risk for maternal morbidity and mortality and fetal demise. Pregnancy in women with Eisenmenger's syndrome is associated with maternal mortality rates from 36% to 39%.[9,84,85] The increased cardiac output and decreased systemic vascular resistance of pregnancy can result in increased right-to-left shunting with worsening cyanosis in patients with Eisenmenger's syndrome (see Chapter 42). Patients with pulmonary hypertension often experience symptomatic deterioration in the second or third trimester and may require hospitalization. Patients can present with fatigue, exertional dyspnea, syncope, chest pain, palpitations, cough, hemoptysis, and leg edema. Premature rupture of membranes is common and should be anticipated.[2,86] Primary pulmonary hypertension is also associated with a high maternal mortality rate, with series reporting rates from 30% to 40%[2,87] and older series reporting rates up to 50%.[85] The increased risk of maternal mortality is seen throughout pregnancy and in the first few weeks following delivery. Death frequently occurs in the early postpartum period and is associated with pulmonary hypertensive crisis, in situ pulmonary artery thrombosis, progressive right ventricular failure, arrhythmias, and sudden death.[2] Recognition of this high maternal mortality rate has led physicians to recommend effective contraception, tubal ligation, and, in the event of pregnancy, early termination.

For patients with pulmonary hypertension who opt to continue a pregnancy, early and prolonged bed rest is recommended.[84] Supplemental oxygen may be helpful. Anticoagulation is recommended throughout gestation (or at least during the third trimester) and in the early postpartum period because in situ thrombosis is a mechanism of maternal demise. Calcium channel blockers, prostacyclins, nitric oxide, and bosentan (an oral endothelin antagonist) are useful therapies for some patients with pulmonary hypertension (see Chapters 42 and 43). Numerous case reports have documented successful use of inhaled nitric oxide and intravenous and inhaled prostacyclins in pregnancy, during labor and delivery, and in the early postpartum period.[86-91]

Avoidance of increases in pulmonary vascular resistance and maintenance of right ventricular preload and contractility are essential in the management of labor and delivery in these patients.[92] Vaginal delivery under epidural anesthesia is recommended. Cesarean section is reserved for obstetric indications because it is associated with greater rates of morbidity and mortality.[93] Oxygen should be administered to minimize hypoxemia, and inhaled nitric oxide or intravenous or inhaled prostaglandins may be used to lower pulmonary vascular resistance. Monitoring in an intensive care unit is recommended for the first several days following delivery.

ENDOCARDITIS PROPHYLAXIS

Antibiotic prophylaxis for bacterial endocarditis is recommended by the American Heart Association for a variety of

dental, respiratory, gastrointestinal, and genitourinary tract procedures if the patient is in a high-risk or moderate-risk category. Patients at high risk for endocarditis include those with prosthetic cardiac valves, a prior history of endocarditis, surgically constructed systemic-pulmonary shunts, and complex cyanotic congenital heart disease. Moderate-risk disease processes include acquired valve dysfunction, such as that associated with rheumatic heart disease; mitral valve prolapse with valvar regurgitation or thickened leaflets, or both; hypertrophic cardiomyopathy; and most other congenital cardiac malformations except for isolated atrial septal defect or repaired atrial septal defect, ventricular septal defect, or patent ductus arteriosus.

Few cases of endocarditis have been associated with delivery. Bacteremia after vaginal delivery was felt to be uncommon, with a reported frequency of 1% to 5%,[14,94,95] compared with rates of 60% to 90% for dental procedures. For this reason, antibiotic prophylaxis is not recommended in the current AHA/ACC practice guidelines for uncomplicated vaginal or abdominal delivery, unless there is suspected bacteremia or active infection.[39] For high-risk patients, prophylaxis during vaginal delivery remains optional. For moderate-risk patients, antibiotics should be administered if complications that increase the likelihood of bacteremia occur during delivery. Many disagree with these guidelines, arguing that complications are usually unexpected and giving antibiotic after a complication occurs exposes a patient unnecessarily. Moreover, reports have documented higher rates of postpartum bacteremia than previous studies, with rates ranging from 14% to 19%.[96-98] Finally, a review of cases of endocarditis complicating pregnancy found significant fetal and maternal mortality rates, 15% and 22%, respectively.[99] Given a higher incidence of bacteremia, the relative low cost of antibiotic prophylaxis, and the major morbidity and mortality of endocarditis, many institutions routinely administer prophylactic antibiotics to moderate- and high-risk patients with valvular and congenital heart disease before delivery.[14] Ampicillin 2.0 g IM or IV plus gentamicin 1.5 mg/kg (not to exceed 120 mg) should be given at initiation of labor or within 30 minutes of a cesarean section, followed by 1 g of ampicillin IM or IV or oral amoxicillin 6 hours later. For penicillin-allergic patients, vancomycin 1.0 g IV is recommended.[39] For moderate-risk patients, a single dose of ampicillin 2 g or vancomycin 1 g is recommended. Practitioners should realize that routine antimicrobial prophylaxis does have its downside. Cost considerations, resultant changes in skin flora with high rates of colonization by resistant staphylococci, and the potential for adverse effects on neonates with resistant bacterial infections must be taken into account when instituting practice guidelines.

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Chapter 42

Care for Adults with Congenital Heart Disease

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CHAPTER CONTENTS

Adult patients with congenital heart disease (ACHD) remain a unique and challenging population in need of cardiac follow-up and care. In the United States this rapidly expanding group is estimated to now exceed its pediatric counterparts, with likely more than 1 million adults with congenital heart disease currently surviving.[1] Longevity and improved well-being can be attributed to increased understanding of cardiac and pulmonary vascular physiology, cardiac embryology and anatomic pathology, as well as improved diagnostic studies and advances in medical therapy, pediatric cardiac surgery, and transcatheter management strategies.[2] Included in the ACHD population are young and older adults who remain unrepaired, those who have undergone palliative procedures such as systemic-pulmonary or cavopulmonary shunts, and those patients who have undergone complete surgical and transcatheter repair with or without known residua (Table 42–1).[3]

We continue to observe an increase in ACHD patient complexity. A shift in improved survival of complicated lesions (tetralogy of Fallot, single ventricle, transposition of the great arteries) has led to patients with such diagnoses receiving a greater percentage of attention from ACHD caregivers. Intensity of medical illness has increased as longstanding atrial, ventricular, and pulmonary vascular volume abnormalities have contributed to increased incidence of arrhythmias, ventricular failure, pulmonary vascular disease, and thrombosis. Close interaction between pediatric and adult cardiologists, cardiovascular interventional catheterizers, cardiac surgeons, and primary physicians is necessary for successful care of ACHD patients, within all levels of regional and local care.[4]

ISSUES FOR THE CARE PROVIDER

Endocarditis

Despite improvements in antibiotic therapy and diagnostic strategies, many adults with congenital heart disease remain at lifelong risk from infective endocarditis. Potential for infection occurs in the setting of structural cardiac lesions that generate turbulent blood flow. Transient bacteremia allows colonization of fibrin/platelet meshwork on the endocardial or prosthetic surface, partially sequestering the organisms from host defenses. Unrepaired defects at greatest risk include high-velocity lesions, such as ventricular septal defects (VSDs) and left-sided stenotic or regurgitant valves. Infective endocarditis is rare in low-pressure lesions, such as mild valvar pulmonary stenosis or in secundum atrial septal defect. After complete surgical repair, endocarditis risk may be significantly decreased, unchanged, or increased due to placement of a prosthetic valve or conduit. A 30-year follow-up study addressed the risk of infective endocarditis after surgery for congenital heart defects.[5] The highest incidence was found in patients after repair of aortic valve stenosis with 20.6% experiencing an episode of endocarditis after 30 years. No cases were reported after repair of patent ductus arteriosus, secundum atrial septal defect, or pulmonary valve stenosis.

A high index of suspicion for the presence of infective endocarditis in adults with congenital heart disease should be maintained due to significantly varied clinical presentations. Patients may have definitive microbiologic data or show the classic manifestations of fever, weight loss, night sweats, splinter hemorrhages, Janeway lesions, and Osler nodes. Others may pose diagnostic challenges. Algorithms that combine clinical criteria with echocardiography may assist evaluation.[6,7] Transthoracic echocardiography may demonstrate vegetations, abscesses, new prosthetic valve dehiscence, or valvar regurgitation. Transesophageal echocardiography has a higher sensitivity for the presence of vegetations and may contribute to diagnostic accuracy.[7] Empiric antibiotic therapy is often initiated in the acutely ill patient while microbiologic data are pending.[8] Therapy for active or presumed infection by common bacterial pathogens is discussed elsewhere in the text.

Patients and other medical care providers should be educated about decreasing the risk for infective endocarditis through the use of established guidelines for antibiotic prophylaxis before undergoing dental, gastrointestinal, or genitourinary procedures.[9] In a survey of adult congenital clinic patients, only 68% were able to identify their own heart condition and 79% understood the necessity for antibiotic prophylaxis of dental procedures.[10] Cardiologists are often asked about the necessity of closing a small ventricular septal defect or patent ductus arteriosus to reduce the chance of developing endocarditis. In the modern antibiotic era, surgical or transcatheter correction of a small hemodynamically insignificant

Table 42–1 Palliative Surgical Procedures and Surgical Repairs

Name	Procedure	Indication	Long-term complications
Palliation			
Blalock-Taussig shunt	Anastomosis of divided subclavian artery to right or left pulmonary artery	Tetralogy of Fallot, single ventricle/pulmonary stenosis	Pulmonary vascular disease, pulmonary artery distortion, ventricular volume overload, decreased ventricular function
Waterston shunt	Ascending aorta to right pulmonary artery anastomosis	Tetralogy of Fallot, single ventricle/pulmonary stenosis	Pulmonary vascular disease, pulmonary artery distortion, ventricular volume overload, and decreased ventricular function
Potts shunt	Ascending aorta to right pulmonary artery anastomosis	Tetralogy of Fallot, single ventricle/pulmonary stenosis	Pulmonary vascular disease, pulmonary artery distortion, ventricular volume overload, and decreased ventricular function
Classic Glenn anastomosis	Superior vena cava to right pulmonary artery anastomosis	Single-ventricle physiology	Pulmonary arteriovenous malformations, cyanosis
Bidirectional Glenn	Superior vena cava to right pulmonary artery anastomosis, pulmonary arteries in continuity	Single-ventricle physiology	Cyanosis
Repair			
Mustard procedure	Atrial baffle	D-transposition of the great arteries	Arrhythmias, decreased systemic right ventricular function, baffle leak, baffle obstruction, abnormal atrial volume conduction
Senning operation	Atrial baffle	D-transposition of the great arteries	See Mustard procedure
Rastelli operation	Intraventricular repair and right ventricle-to-pulmonary artery conduit	D-transposition of the great arteries/ventricular septal defect/left ventricular outflow tract obstruction	Conduit obstruction, myocardial dysfunction, arrhythmia
Fontan procedure	Atriopulmonary or total cavopulmonary connection for separation of systemic and pulmonary circulations	Tricuspid atresia, single-ventricle physiology	Arrhythmia, thrombus, protein-losing enteropathy, atrial distortion and abnormal volume conduction, baffle leak
Ross operation	Aortic valve replacement with native pulmonary valve, pulmonary homograft	Aortic stenosis, aortic regurgitation	Pulmonary regurgitation, homograft obstruction, aortic regurgitation
Konno operation	Aortoventriculoplasty	Tunnel subaortic stenosis	Recurrent subaortic stenosis
Arterial switch operation	Anatomic correction with coronary transfer	D-transposition of the great arteries	Supravalvar pulmonary stenosis, supravalvar aotic stenosis, dilation of neoaortic root
Damus-Kaye-Stansel operation	Arterial level repair without coronary transfer	Double-outlet right ventricle (Taussig-Bing type/ subaortic stenosis, D-transposition of the great arteries and coronary pattern not appropriate for transfer)	Native aortic regurgitation, thrombosis in coronary arterial blind pouch
Takeuchi procedure	Intrapulmonary baffle of anomalous coronary artery from the pulmonary artery	Anomalous left coronary artery from the pulmonary artery	Baffle obstruction or leak, supravalvar pulmonary stenosis

ventricular septal defect or patent ductus arteriosus with the primary intent to decrease or eliminate subacute bacterial endocarditis (SBE) risk is not recommended.[11]

Left-to-Right Shunting: General Principles

Patients with the potential for left-to-right intravascular recirculation of arterial blood into the systemic venous circulation pose challenges for health care providers because of the risk of volume overload and the development of congestive heart failure. These shunts depend on both the presence of a physical passage between the arterial and venous circulations, as well as differential resistance to flow within these circuits. Capacitance and resistance to filling in the most proximal downstream chamber or vessel to the existing shunt is the most important determinant of direction and extent of flow. Increased left-to-right shunt flow depends on decreased vascular or ventricular compliance or increased pressure and increased systemic vascular resistance as may occur in the setting of aging, stress, heart failure, and certain hypermetabolic states. Decreased shunting may result from a fall in arterial resistance as occurs in pregnancy, sepsis, and endocrinologic illness. The results of acute volume loss can be mixed on the basis of the effects of decreased blood pressure (BP) versus increased systemic vascular resistance. Assessment of chronic shunting is better performed once such conditions have been corrected. Regardless of the nature and extent of intravascular shunting, and even with predominant left-to-right shunting, the potential for right-to-left passage of even a minute quantity of blood at some phase of the cardiac cycle typically exists. Therefore precautions such as intravenous catheter filtering of particulate or gaseous material should be used.

Cyanosis

Cyanosis is the dark blue discoloration of skin and mucous membranes caused by increased amounts of reduced or abnormal hemoglobin in cutaneous blood vessels. Underlying pathology, extent of skin pigmentation, keratinization, and capillary density may influence the degree of cyanosis. Cyanosis may fluctuate due to alterations in hematologic parameters, as well as changes in cardiovascular, pulmonary, and renal function. Sequelae of long-term cyanosis occur in virtually all organ systems and may have profound consequences.

Generally, clinically evident cyanosis is seen at an arterial saturation of approximately 85%, although in patients with dark skin pigmentation, cyanosis may not be recognized until considerably lower oxygen saturations. Cyanosis most frequently encountered by the physician caring for adults with congenital heart disease is caused by right-to-left intravascular shunting of systemic venous blood into the systemic arterial circulation. This situation depends on either physical obstruction of pulmonary blood flow or elevation of pulmonary vascular resistance. Increased pulmonary vascular resistance may be transient and reactive to secondary stimuli including oxygen, acetylcholine, prostaglandin (PGE1), prostacyclin (PGI2), or nitric oxide or may be more "fixed" with increased arteriolar muscularity, intimal hyperplasia, and decreased numbers of intra-acinar arteries.[12] Major congenital lesions that may present with cyanosis in adulthood include unoperated lesions, such as tetralogy of Fallot and its variants; Ebstein's anomaly; and patients with single ventricle physiology, either repaired or after a palliative procedure. Additionally, patients with unrepaired left-to-right shunt lesions may present with cyanosis secondary to reversed shunting in the presence of elevated resistance or the Eisenmenger syndrome.[13]

Major Cyanotic Organ Complications

Musculoskeletal Changes

The presence of clubbing is a significant accompaniment to central cyanosis. This is a flattening of the nail beds, which causes loss of the normal 160-degree angle between the base of the nail and the adjoining skin.[14] Clubbing is a component of hypertrophic osteoarthropathy, a clinical syndrome that also includes periostosis and joint swelling. The severity of clubbing varies with extent of cyanosis and, in the setting of differential cyanosis, is found only in the cyanotic region. Histologic findings associated with clubbing include dilation and thickening of vascular walls, an increase in blood vessel–associated connective tissue and the development of multiple tiny arteriovenous connections.[14,15] Additionally, increased thickness of the periosteum is observed along with increased bone resorption.

Hematologic Changes

Arterial oxygen content in cyanotic individuals is maintained by compensatory changes in hemoglobin concentration; 2,3,DPG levels; and cardiac output. Increased production of erythropoietin is triggered by tissue hypoxia, which produces an increase in erythrocyte mass and blood volume. This improves oxygen-carrying capacity by increasing hemoglobin; however, extreme elevations in hematocrit may result in symptoms of hyperviscosity.[17] Hyperviscosity syndromes may present as headache, visual changes, mild paresthesias, fatigue, or musculoskeletal symptomatology.[16] Iron deficiency due to reduced deformability of microcytic red blood cells also contributes to increased blood viscosity.[18] Additionally, diminished iron stores affect tissue oxygen delivery as evidenced by a more right-shifted oxyhemoglobin dissociation curve.

Cyanotic patients may be divided into two categories: "compensated" and "decompensated" erythrocytosis.[19] "Compensated" patients are iron replete, have stable volume status and hematocrit, are in multiorgan system balance, and do not experience symptoms of hyperviscosity. "Decompensated" patients are iron deficient and have continually rising hematocrits often due to episodic identifiable and correctable influences (dehydration, acute increase in right-to-left shunting or pulmonary resistance, heart failure, infection, or central nervous system events.) These patients experience symptoms of hyperviscosity requiring phlebotomy that may further increase iron deficiency. Correction of the underlying influence is the primary treatment. Isovolumic phlebotomy is advised only for hyperviscosity symptoms in patients with hematocrit typically greater than 65 gm/dL when adequately hydrated and after correction of potential precipitating factors. Phlebotomy is not advised for an isolated elevation of the hematocrit in "compensated" patients without symptoms. Iron repletion in cyanotic patients should be undertaken with close monitoring to prevent rebound erythrocytosis and hyperviscosity.

An increased tendency for perioperative bleeding has long been recognized in patients with cyanotic congenital heart disease, and numerous abnormalities of hemostasis have been reported in this population. These have included prolonged

prothrombin time, thrombocytopenia, impaired platelet aggregation, and shortened platelet survival. In some individuals, the problem may be compounded by deficiency of vitamin K–dependent clotting factors due to altered hepatic function in the setting of passive congestion secondary to chronic heart failure. The use of anticoagulants and antiplatelet agents in the cyanotic patient has been controversial; however, no data exist to support the increased risk of bleeding associated with long-term anticoagulation. Chronic anticoagulation is typically prescribed if other standard indications, such as atrial fibrillation or a mechanical prosthetic heart valve, are present.

Renal Changes

Abnormalities of renal function are frequently recognized in patients with cyanotic heart disease. Urinalysis results suggesting glomerulopathy have been noted to occur in up to one third of a population of adults with cyanotic congenital heart disease.[20] Associated renal pathology takes the form of altered glomerular architecture including focal glomerular sclerosis, congestion, and mesangial hypercellularity, as well as disorders of renal function. Cyanotic patients have been shown to exhibit decreased glomerular filtration rates, proteinuria, and impaired water handling. Renal dysfunction may be compounded by the use of long-term diuretic therapy or associated decreased ventricular function. Reduction of concomitant risks for acute renal dysfunction, such as ensuring adequate hydration, and dosing medications based on estimates of glomerular filtration rate are advised.

Gout has long been associated with cyanotic heart disease. Cyanotic patients have been found to have increased serum uric acid levels due to decreased fractional urate excretion rather than to increased production. Cornerstones of symptomatic management of acute gouty arthritis in cyanotic patients include the use of colchicine (0.5 to 0.6 mg po Q1 to 2 hours) and corticosteroids (40 to 60 mg PO QD). Nonsteroidal anti-inflammatory agents are generally not preferred as first-line agents due to potential deleterious effects on renal function. Maintenance therapy (allopurinol 100 mg PO QD) may be required for recurrent episodes, although allopurinol may exacerbate decreased renal function as well.

Cardiopulmonary Exercise

Decreased ventricular function has been described in cyanotic patients with persistence after repair in some groups, although causation remains unclear.[22] Contributing factors include age at repair, extent of cyanosis, and the presence of pressure or volume overload. Potential mechanisms for ventricular dysfunction secondary to cyanosis may involve myocardial hypoxia with oxygen demand exceeding supply, as well as altered coronary perfusion due to erythrocytosis, resulting in myocardial necrosis and fibrosis.

Cyanotic patients have been noted to have increased dyspnea on exertion, as well as decreased exercise tolerance. Patients with single-ventricle physiology have been shown to have significant exercise limitations as determined by decreased exercise time, total work performed, peak heart rate, peak oxygen uptake, and arterial oxygen saturation.[23] In normal persons, oxygen demand and CO_2 production are closely matched by circulatory and respiratory changes during exercise. Right-to-left shunting produces changes both in oxygen uptake and ventilation. During exercise, cyanotic patients show decreased oxygen uptake, as well as a delay in establishment of a steady state. In addition, cyanotic patients exhibit higher exercise ventilation than control patients.[24] Presumably, this occurs as a result of increased pCO_2 and hydrogen ion concentration in the systemic arterial system from right-to-left shunting.

Neurologic Effects

A variety of neurologic effects are associated with the presence of chronic cyanosis due to right-to-left shunt lesions. The ability of blood flow to bypass the pulmonary circulation leads to the possibility of embolization to the cerebral circulation of substances that might have been filtered in the lungs. Cyanotic patients are therefore at risk for brain abscesses from septic embolization, as well as for cerebral vascular accidents precipitated by migration of thrombus, air, or foreign particles.[25] The physician should have a low threshold for obtaining brain imaging in the setting of a patient with a fever, headache, or fixed and localizing neurologic signs. Importantly, the differential diagnosis in a cyanotic patient with transient neurologic symptoms includes transient ischemic attacks and infection, as well as hyperviscosity.

Longstanding cyanotic congenital heart disease has been associated with intellectual impairment,[26] decreased school performance, and difficulties with social adaptation including persistence of a dependent lifestyle. However, confounding variables in establishing the effect of cyanosis on social and intellectual functioning include the possible contributions of cardiac surgery and circulatory arrest, the psychological effects of chronic illness, and the influences of parental and societal attitudes given the severity of illness. Throughout life, every potential response to limit and understand these effects should be made to bolster independence and self-confidence.

Recommendations for Management of the Cyanotic Patient

Recognizing and correcting any secondary situations that may provoke increased cyanosis, regardless of underlying congenital pathology, is important. Infection, dehydration, or erythrocytosis can all increase cyanosis. Other precipitants include worsening ventricular function, ischemic myocardial changes, increased atrioventricular valvular regurgitation, increased pulmonary hypertension, and alteration in renal or hepatic function. Not routinely resorting to phlebotomy for increased cyanosis without a search for other correctable causes is also important. Anemia or iron deficiency may cause profound fatigue and worsening symptoms of hyperviscosity. In addition to alleviation of intercurrent illness, therapeutics must be based on a thorough understanding of the underlying pathology causing cyanosis.

In general, steps should be made to increase the amount of oxygen in the blood. This may be performed by improving oxygen-carrying capacity by increasing the hematocrit, by the administration of oxygen if oxygen saturation is low, improving ventilation if pCO_2 is high, and by judicious choice of methods to optimize volume status. Tissue perfusion and oxygen extraction help determine oxygen content of mixed systemic venous blood. Abnormalities of both (e.g., decreased tissue perfusion with profound dehydration or increased oxygen extraction with systemic ventricular failure) may lead to decreased oxygen content of mixed systemic venous blood.

In the setting of intracardiac shunting these changes may account for acute or chronic increases in cyanosis. Thus depending on the clinical situation, patients may need either volume expansion or diuresis.

Augmentation of pulmonary blood flow should use methods to decrease pulmonary vascular resistance. Appropriate measures may include administering oxygen; eliminating acidosis; and the use of specific pulmonary vasomodulators, such as nitric oxide, bosentan, sildenafil, or prostanoids.[27] The use of home oxygen therapy has been suggested to improve pulmonary blood flow in patients with irreversible pulmonary vascular disease.[28] Only open-label trials have been performed with therapies including continuous IV prostacyclin[29,30,31] and continuous inhaled nitric oxide.[32]

Cyanosis may be lessened by improvement in ventricular function. This will occur on optimizing forward cardiac output and improving mixed venous O_2 saturation. Additionally, the use of angiotensin-converting enzyme (ACE) inhibitors even in patients with intracardiac shunting[33] may help to maximize ventricular function, particularly in cases with atrioventricular valvular regurgitation where afterload reduction enhances output. In the critically ill patient, the use of IV agents such as isoproterenol, milrinone, dobutamine, and nitroprusside may prove efficacious, although they have not been studied.

Concern arises about the ability of cyanotic patients to tolerate the reduction of partial pressure of oxygen produced during commercial airline flights.[35] Similar to native residents of high altitude, patients with congenital cyanotic heart disease have been shown to have a decreased ventilatory response to acute hypoxia. This has been shown to return to normal after surgery correcting the cyanosis. These data suggest difficulty in acute respiratory accommodation to atmospheric changes accompanying flight. We recommend minimization of cyanosis before flights if travel is desired or necessary. Metabolic demands and stress should be reduced, with utilization of baggage and transportation assistance coordinated with early airport arrival. Adequate preflight and in-transport rest, nutrition, and hydration are emphasized. Supplemental oxygen is provided at levels of baseline use to maintain oxygen saturations > 80%. If oxygen saturations are below 70% despite supplemental oxygen, even slight unexpected decremental changes might place a patient in jeopardy and air travel would not be recommended.

Pregnancy

Reproductive issues are of major concern for the growing population of young women with corrected or palliated congenital heart disease. Successful counseled and planned childbearing for women and men with congenital heart disease is currently the rule, with limited exceptions as discussed later. In advising such patients, the cardiologist must be familiar with both the physiology of existing cardiac lesions in the gravid state, as well as with contemporary guidelines for genetic screening of cardiac defects. Optimal care is provided in a comprehensive center by a team of specialists including cardiologists, high-risk obstetricians, anesthesiologists, fetal echocardiographers, and geneticists.

Hemodynamic changes occurring in pregnancy may have significant consequences for the patient with congenital heart disease. Increased blood volume, stroke volume, and heart rate lead to augmented cardiac output in the antepartum period. Decline in systemic vascular resistance due to hormonal influences may result in increased right-to-left shunting. The physiologic anemia of pregnancy may exacerbate preexisting difficulties with tissue oxygen delivery. Labor and delivery are accompanied by hemodynamic shifts from pain, uterine contractions, anesthesia effects, and bleeding.

Pregnancy outcomes for women with specific congenital heart defects have been detailed in a number of published reports.[35-38] However, most existing data regarding risks and success of pregnancy in congenital heart disease are anecdotal and may have changed with newer therapeutics. Ongoing efforts are directed at the development of tools for risk stratification of pregnancy-related complications in women with cardiac defects. A retrospective cohort study examined 276 pregnancies in 221 women with heart disease receiving obstetrical care at three major institutions from 1986-1994. Multivariate analysis identified five independent predictors of maternal cardiac events.[39] These included (1) prior cardiac events, (2) prior arrhythmia, (3) New York Heart Association (NYHA) functional class > II or cyanosis during the baseline antenatal visit, (4) left heart obstruction, and (5) myocardial dysfunction. Maternal NYHA class > II or cyanosis during the initial visit independently predicted neonatal complications such as prematurity, respiratory distress syndrome, and small-for–gestational age birth weight. Additionally, a higher proportion of pregnancies ending in miscarriage was found in mothers in each of these two groups. Additive peripartum risk was seen with maternal subpulmonary ventricular dysfunction, in analysis of a separate large congenital heart–specific pregnancy database and similar risk scale assessment.[40] Of note, in neither of the previously mentioned databases were patients with severe pulmonary hypertension enrolled in the study. However, most centers caring for patients with severe fixed pulmonary hypertension (primary or secondary, with or without intracardiac shunting) would argue that such patients carry prohibitive maternal risk of morbidity and mortality.[41] Even in the current era, maternal mortality in patients with the Eisenmenger syndrome approaches 36%.[42]

Recommendations for Managing the Pregnant Patient

If possible, women with congenital heart disease of childbearing age should undergo a comprehensive preconception evaluation including determination of ventricular function, assessment of left heart obstruction, examination for right-to-left shunting, and review of arrhythmias. Analysis of current medications should identify those contraindicated during pregnancy, with particular attention to warfarin and ACE inhibitors. Genetic counseling including karyotype examination or fluorescence in situ hybridization for microdeletion of chromosome 22 should be provided for patients with congenital heart disease, not only for those with identified hereditary defects. Patients are advised that cardiac fetal echocardiography at 16 to 20 weeks' gestation may allow early identification of potential fetal cardiac malformations.

Throughout pregnancy, patients should be followed at regular intervals. In our practice, we evaluate patients at least once during each trimester of pregnancy. Causes of increased cyanosis should be investigated and heart failure should be promptly treated. Strategies that may be employed during

labor and delivery, if necessary, include the use of early epidural anesthesia to control pain and avoid major alterations in systemic vascular resistance, the provision of supplemental oxygen, shortening the second stage of labor, and the employment of techniques designed to decrease volume shifts. The need for cardiac monitoring and/or pulmonary artery catheters should be evaluated on an individual case basis. Vigilance should be heightened in the first 48 hours (and at times up to several weeks) post partum with particular attention to fluid management, hemodynamic status, pulmonary vascular resistance, and potential for thromboembolism. The use of anticoagulant therapy to prevent thrombotic complications in the third trimester and postpartum in patients with right-to-left shunts is controversial. American Heart Association guidelines do not recommend endocarditis prophylaxis for uncomplicated vaginal deliveries or Cesarean section, although many centers deviate from this guideline in practice.[9]

Noncardiac Surgery

The primary cardiologist is often requested to assist in the management of adults with congenital heart disease undergoing noncardiac surgery. Recommendations must be individualized for particular patients and surgeries. A retrospective cohort study examined perioperative morbidity and mortality for 276 adults and children with congenital heart disease undergoing noncardiac surgical procedures.[43] Major risk factors associated with complications included the presence of cyanosis, congestive heart failure, and poor general health. Noncardiac surgical procedures in patients with Eisenmenger syndrome are associated with increased risk for complications.[44]

Recommendations

The primary cardiologist should actively assist in perioperative management decisions. Anesthetic induction regimens should be chosen with regard to their effects of maintaining oxygen saturation, as well as for hemodynamic stability.[45,46] Basic tenets of operative management for patients with shunts include avoiding acute increases or decreases in systemic vascular resistance, which may have important effects on shunt flow and systemic perfusion. Particular vigilance to avoid deep venous thrombosis and paradoxical embolism is warranted—all IV devices should include filters to prevent introduction of air or particles. Appropriate preoperative sedation, as well as postoperative pain control, should use agents that do not lower systemic venous resistance. Because hypovolemia will increase shunting and lower arterial oxygen saturations, patients should be carefully monitored for postural BP swings resulting in increased cyanosis. Scrupulous attention should be paid to control of blood loss and monitoring of the postoperative hematocrit.[46] Antibiotics should be administered according to American Heart Association guidelines for SBE prophylaxis (see Chapter 44).[9] Consideration should be given to overnight observation in intensive care settings for all but minor procedures. Procedures involving potential for marked changes in relative pulmonary blood flow should be performed in centers with expertise in acute IV and inhaled pulmonary vasodilators and ready access to extracorporeal membrane oxygenation support, ventricular assist devices, and organ transplantation.

Arrhythmia

Adults with congenital heart disease are at increased risk for both atrial and ventricular arrhythmias due to longstanding volume load, increased afterload, multiple surgical scars, and myopathic ventricles. Issues of arrhythmias associated with atrial septal defects and repaired tetralogy of Fallot are addressed later in this chapter. Various risk assessment strategies have been suggested to identify ACHD patients at risk for acute tachyarrhythmias and sudden death. Programmed ventricular stimulation (VSTIM) in a selected group of congenital heart disease patients has been used to identify a subgroup with decreased and increased risk of serious arrhythmic events.[47] VSTIM studies were performed on 140 patients with CHD with indications including spontaneous ventricular tachycardia or symptoms of arrhythmia; 38% of these studies were termed "positive" due to induction of sustained or nonsustained ventricular tachycardia. By multivariate analysis, positive VSTIM studies in this population were associated with sixfold increased mortality and threefold increased risk of sudden arrhythmia. However, 33% of patients with previously documented ventricular tachycardia had false-negative test results, thus limiting ability to predict outcome in patients without inducible arrhythmias during a VSTIM study.

Management strategies include antiarrhythmic drugs, transcatheter radiofrequency ablation, surgical maneuvers, and pacemaker or implantable telemetry monitoring for development of proarrhythmia, negative inotropic effects, or symptomatic bradycardia requiring pacemaker placement. Radiofrequency catheter ablation has been successfully used for control of arrhythmias with congenital heart disease and may provide years of freedom from the use of antiarrhythmic medications in selected patients.[48] Similarly, right- or left-sided Maze procedures have been effective in reducing incidence of atrial tachyarrhythmias if performed at the time of cardiac surgical repair.[49] Indications for prophylactic atrial or ventricular pacing, in single or multiple sites, to diminish arrhythmia and to improve atrial or ventricular function require further study.

Exercise and Athletic Participation

Adult survivors of congenital heart disease frequently raise questions about exercise limitations or benefits, or both. A survey of adults at a tertiary referral clinic for congenital heart disease demonstrated considerable patient confusion regarding the appropriate level of exercise for existing cardiac lesions.[50] Exercise tolerance and cardiorespiratory responses to exercise were studied in three groups of adult patients enrolled in the Second Natural History Study of Congenital Heart Defects.[51] Mean exercise duration was below normal at 94.2%, 90.8%, and 86.5% of predicted for patients with pulmonary stenosis, ventricular septal defect, or aortic stenosis, respectively. Several studies have examined the effects of surgical repair of selected cardiac defects on cardiopulmonary exercise capacity. Adults with unrestrictive atrial septal defect demonstrated significantly reduced preoperative cardiopulmonary exercise capacity.[52] At early postoperative follow-up (4 months), slight improvement was present with complete return to normal tolerance 10 years postoperatively. Functional exercise capacity after atrial septal closure is inversely correlated with age at operation.[53] Patients with Ebstein's anomaly

of the tricuspid valve have a reduction in exercise tolerance, which is improved after definitive repair.[54] Patients who have undergone the Fontan operation for tricuspid atresia or single ventricle have considerably lower maximal workload, anaerobic threshold, and maximal oxygen consumption than normal volunteers despite clinical presentation as NYHA functional class I or II.[55] To date, adults with congenital heart disease remain a paradigm for the multitude of comorbidities that combine to engender functional incapacity.[24]

Studies of physical training in patients with severe left ventricular dysfunction have demonstrated that supervised exercise conditioning can produce increased peak oxygen consumption, improve cardiac output, decrease resting heart rate, increase skeletal muscle blood flow, delay lactate accumulation during exercise, and improve sense of well-being.[56] Extrapolation from such data suggests that adult patients with congenital heart disease may benefit from regular aerobic conditioning, which may increase peripheral extraction and hence decrease myocardial work and increase functional capacity. Postoperative exercise training has been shown to benefit children after surgery for congenital heart disease by improving their fitness level.[57,58] However, the safety and utility of exercise rehabilitation programs for adults with congenital heart disease is not known.

Recommendations for athletic participation of adults with congenital heart disease are in evolution. Conservative restrictive guidelines can be extrapolated from the American College of Cardiology consensus statement.[59] Strenuous exercise is most restricted in adults with illnesses when experience has suggested catastrophic potential with exertion. These include severe systemic ventricular outflow obstruction, severe pulmonary hypertension (with near-systemic pulmonary artery BP), aortic root dilation > 4.0 to 4.5 cm, single coronary artery or fixed coronary obstruction, sustained or exercise-induced ventricular arrhythmia, systemic or pulmonary ventricular failure, or pulse oximetry saturation < 70%. Practically, in all other cases, given marked individual variation, we recommend reproduction of the desired level of strenuous exercise under physiologic monitoring. This should include measurement of transcutaneous oxygen saturation; $\dot{V}O_2$ max; anaerobic threshold; VE/VCO_2; duration of exercise and observation for electrocardiographic evidence of arrhythmia or ischemia; and echocardiographic assessment of transvalvar gradient, ventricular function, and pulmonary artery pressure. Risks and goals of athletic participation are then openly discussed with patients and family members.

Transplantation

Cardiac transplantation for congenital heart disease is offered for indications including (1) native cardiac anatomy not amenable to repair or palliation and (2) severe ventricular dysfunction after attempted repair.[60-62] Patients referred for consideration of cardiac transplantation benefit from joint management between adult congenital heart disease specialists and the cardiac transplant team. In some cases it is possible to avoid transplantation after optimizing medical or interventional therapy, or both. Patients considered to be appropriate candidates for transplantation include those with (1) progressively decreased ventricular function despite ongoing medical treatment, (2) requirement for IV inotropic support, (3) malignant arrhythmias unresponsive to standard medical or electrophysiologic treatment including attempted transcatheter ablation or automatic implantable cardioverter-defibrillator placement, and (4) unacceptable quality of life.[60] Complications of cardiac transplantation unique to patients with ACHD include the risk of bleeding after reoperation, adherence of structures to the sternum in patients with previous surgeries, technical difficulties posed by complex anatomy, and recipient sensitization to MHC antigens from multiple previous blood transfusions resulting in higher rates of graft rejection.[60,63]

Preoperative pulmonary hypertension conveys significant risk for post-transplant right heart failure and mortality.[64] In an era before widespread use of effective inhaled or IV pulmonary vasodilators, oral endothelin antagonists and phosphodiesterase inhibitors, and right ventricular (RV) support, patients with initial pulmonary vascular resistance > 2.5 Wood units (comparable with > 100 to 140 dynes-sec·cm^{-5}) were found to have a 3-month mortality rate of 17.9% compared with 6.9% in patients with resistances less than 2.5. All patients undergoing pretransplant evaluation should undergo assessment of pulmonary pressures with pulmonary vasodilator testing if raised pressures are diagnosed.[65] Patients with congenital heart disease and pulmonary artery resistance greater than 8 to 10 Wood units (comparable with 320-540 dynes-sec·cm^{-5}) may be considered for lung or heart/lung transplantation.[66,67] Single-lung transplantation with concomitant cardiac repair has been successfully performed in patients with end-stage pulmonary hypertension secondary to Eisenmenger syndrome; and recovery of impaired RV function has been demonstrated after transplant.[68] Considerations of heart/lung transplantation are generally reserved for patients with increased pulmonary vascular resistance as outlined earlier in addition to left ventricular dysfunction or complex intracardiac anatomy.

GUIDELINES FOR MANAGEMENT OF PATIENTS WITH SPECIFIC CONGENITAL CARDIAC LESIONS

Atrial Septal Defects

Atrial septal defects are congenital defects that allow communication between the left and right atria (Fig. 42–1). Atrial septal defects are typically classified as secundum-type (2-ASD), ostium-primum (1-ASD), sinus venosus, and coronary sinus defects. 2-ASDs comprise approximately 10% of all isolated congenital heart malformations and more than 75% of all ASDs.[69] Embryologically, the defect appears to stem from abnormal development of the septum primum, resulting in a failure to cover the fossa ovalis. 1-ASDs are a form of endocardial cushion defect almost always associated with abnormality of atrioventricular valve formation (in its most benign form "cleft" anterior leaflet of the mitral valve). Sinus venosus defects are located at the entrance of the superior vena cava to the right atrium and are frequently associated with "anomalous" right upper pulmonary venous drainage to the SVC-right atrial junction. They comprise 10% of all atrial septal defects and, compared with other ASDs, sinus venosus type ASDs are more commonly associated with elevation of pulmonary vascular resistance if left untreated. The least common type of ASD is the "unroofed" coronary sinus, which results in a connection between the coronary sinus and the left atrium.

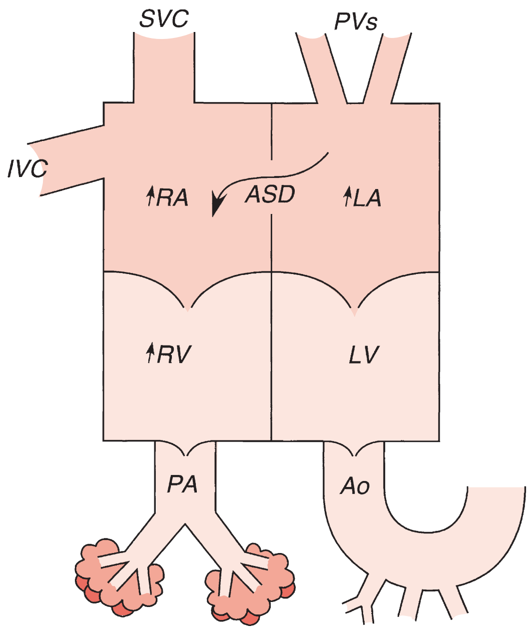


Figure 42–1 ASD physiology. Intracardiac shunting is governed by relative resistance to ventricular filling. Unless RV function is compromised, flow is left to right with enlargement of right-sided chambers. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

Physiologically, the direction and amount of shunting across an ASD depends on the size of the ASD, the respective right- and left-sided chamber compliances, and downstream arterial vessel resistances. Normally, the physiologic parameters are such that shunt flow is from left to right. Over time left-to-right shunting results in volume overloading and ultimately dilatation of the right-sided chambers. We rely primarily on physiologic confirmation of excessive RV volume loading by echocardiography, rather than primary catheterization-based documentation of significant shunting(pulmonary/systemic flow ≥1.5) as evidence of a hemodynamically "significant" shunt, although the superiority of this assessment in predicting clinical morbidity is unproven. We do not perform "routine" catheterization of patients with ASD for determination of intracardiac shunting. Transesophageal echocardiography or MRI, or both, are useful in further defining the location and size of the defect, right-sided chamber sizes, and associated anomalies such as anomalous pulmonary venous drainage.

Large shunts (Qp:Qs > 1.5 to 2.0) increase the risk for dyspnea; congestive failure; atrial arrhythmias; and, less commonly, pulmonary hypertension or paradoxical embolization. Increased shunting may occur with increasing patient age due to decreasing left ventricular compliance associated with aging, systemic hypertension, diabetes mellitus, obesity, and ischemic heart disease. All secondary influences on shunting should be medically minimized before assessing the importance of an ASD. Endocarditis prophylaxis is not recommended for isolated 2-ASDs. Although pregnancy is well tolerated in patients with 2-ASD and even a moderate degree of intracardiac shunting, there remains controversy concerning the need to close such defects before childbirth theoretically to decrease the rare risk of paradoxical embolization through this defect. We do not recommend ASD closure without hemodynamic indication.

Although somewhat controversial, symptomatic patients with large left-to-right shunts appear to have decreased symptomatology and atrial arrhythmias and improved longevity with ASD closure.[70,71] Although surgical patch or primary suture closure (with or without minithoracotomy) of ASDs remains one of the safest and most effective of adult cardiac surgical procedures, significant morbidity may ensue. Increasing age (with medical comorbidities) and the presence of pulmonary hypertension are independent risk factors for increased surgical mortality. Surgical success is generally uniform yet may be accompanied by minor but persistent shunting detectable in upwards of 7% to 8% of surgically treated patients by echocardiography.[72] The incidence of major or minor neuropsychiatric complications after cardiopulmonary bypass in this population has focused attention on transcatheter closure techniques.

In 1959 Hufnagel and Gillespie were the first to implant a device, or plastic button, on the atrial septum (via thoracotomy) to accomplish ASD closure.[73] The first intracardiac use of a double-umbrella–type device was pioneered by King and Mills in 1974.[74] Device design was refined by Rashkind in 1983 to resemble a barbed single disc and later modified to become a more flexible double disc.[75] Lock and colleagues[76] altered the wire configuration to allow springed joints on the device arms, forming the first of the modern "clamshell" varieties of closure devices. Subsequent device modifications (CardioSEAL-STARFlex, NMT Medical, Boston) have incorporated changes in device arm alloy (MP35N) to allow MRI compatibility, adding a second spring to each arm (to reduce and displace device-mediated cardiac stress and lower device profile), and to place nitinol microspring arms in a central interconnecting arm-to-arm mesh (to allow for auto-adjustment and maximal defect closure), as well as creating devices with bioabsorbable potential (Biostar, NMT Medical, Boston). However, double-umbrella devices have not received. Food and Drug Administration (FDA) approval for implantation to close atrial septal defects and therefore are typically used only for small- to moderate-sized (<12- to 14-mm maximal stretch diameter) secundum (2)–type ASDs, in off-label fashion after specific patient–physician discussion. Various types of currently implanted intracardiac closure devices are shown in Figure 42–2.

The only device approved by the FDA for catheter closure of 2-ASDs (for all age groups including pediatrics) is the Amplatzer Septal Occluder (ASO) device (AGA Medical Corp, Golden Valley, Minn). This device is constructed from a 0.004 to 0.0075 nitinol wire mesh, tightly woven into two flat discs (LA disc larger than RA disc), with a 3- to 4-mm connecting waist separating the two discs (with three Dacron polyester patches sewn into the discs and connecting waist, respectively, to increase "thrombogenicity"). The wire mesh can be stretched to form a single wire configuration (allowing transport within a guide catheter-delivery system), although original shape is reformed on deployment due to the memory properties of nitinol. Under FDA requirement, operators must be proctored at their own institutions before achieving independent implanter status.

For potential closure of 2-ASD with all approved and investigation closure devices, the atrial septum can be readily crossed from femoral venous access (on occasion, internal jugular or hepatic venous access may be used). The placement

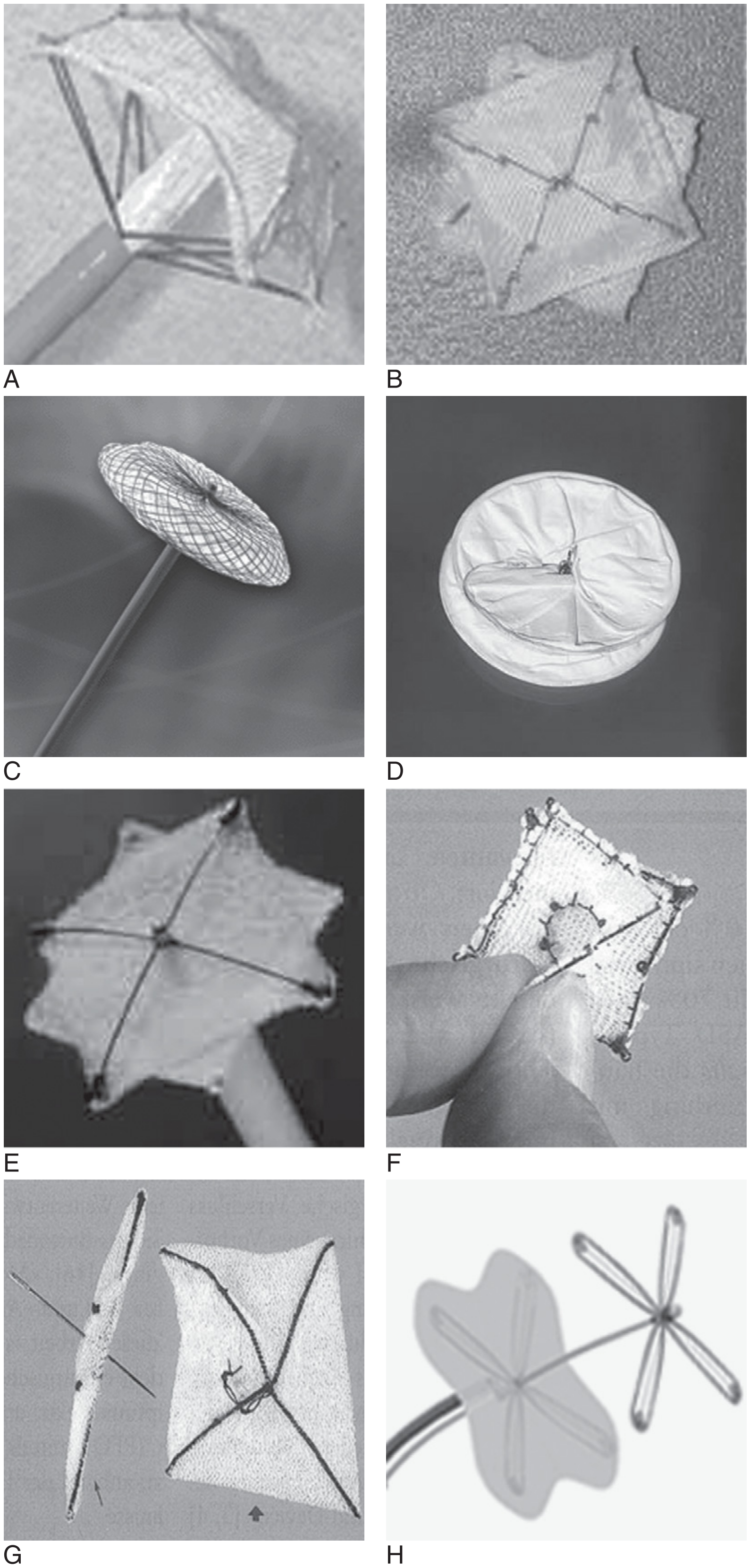


Figure 42–2 Currently implanted intracardiac closure devices. **A,** CardioSEAL-STARFlex (Nitinol Medical Technologies, Boston). **B,** CardioSEAL (Nitinol Medical Technologies, Boston). **C,** Amplatzer PFO Occluder (AGA Medical, Golden Valley, Minn). **D,** Helex occluder (W.L. Gore and Associates, Inc., Flagstaff, Ariz). **E,** PFO-Star (CARDIA, Burnsville, Minn). **F,** Guardian Angel (Microvena Corporation, White Bear Lake, Minn). **G,** Sideris Buttoned Device (Custom Medical Devices, Amarillo, Texas). **H,** Premere Device (St. Jude Medical, Inc., St. Paul, Minn).

of a large-caliber guiding sheath allows precise extrusion of compacted expandable devices in the desired location (Fig. 42–3). The majority of septal closure devices are designed as locked or attachable opposing structures that engage the rim of the tissue surrounding a central hole in the heart wall. Routine use of transesophageal echocardiography has been supported by increasing use of intracardiac echocardiography (ICE), and both greatly assist in appropriate device arm placement and success at defect closure.[77]

Clinical experience is greatest with the ASO devices, although in appropriate centers of expertise, results appear similar with various implants including off-label CardioSEAL

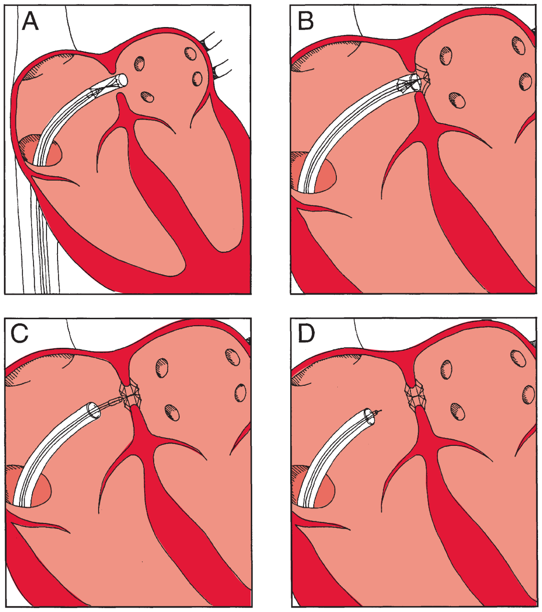


Figure 42–3 Technique of transcatheter deployment of Clamshell occluder for secundum-type atrial septal defect closure.

and investigational HELEX Septal Occluder (Gore Medical Products, W.L. Gore & Associates, Inc., Flagstaff, Ariz) devices.[78-80] Closure rates should typically achieve approximately 95% complete success for centrally located defects, with a < 1% to 7% complication rate and 0% mortality.[78-80] Device-related thrombosis or atrial perforations have been recently highlighted but are uncommon.[81,82] A typical postimplantation medical regimen includes aspirin 325 mg daily for at least 6 months with concomitant clopidogrel and 75 mg daily for 2 to 3 months, although data supporting such recommendations remain theoretic. Antibiotic precautions surrounding dental work or "dirty procedures" are recommended for the maximum of at least 6 months or until no residual bubble contrast shunting is recognized on transthoracic echocardiography.

Recommendations

We recommend closure of ASDs in the presence of echocardiographic evidence of RV volume loading (generally correlating with Qp/Qs > 1.5) that cannot be explained by concomitant confounding intracardiac pathology (e.g., pulmonary regurgitation, tricuspid regurgitation, or anomalous pulmonary venous return). We do not routinely measure Qp/Qs as a determinant for ASD closure. Surgical options are among the most successful of modern cardiac surgical procedures but still carry associated morbidity. 2-ASDs < 36 mm in stretch size (though typically < 32 mm stretch size) are most amenable to transcatheter device closure, though significant diastolic dysfunction and tendency to volume retention may remain. Greatest worldwide experience is with the self-centering Amplatzer ASO device for moderate to large 2-ASDs. This has become a standard of care as therapy. Nickel allergy, device thrombosis, and device-cardiac interaction (as evidenced by potential for early and late device erosions and as residual diastolic abnormalities) highlight the need for more subtle, compliant, and absorbable devices that will likely be fashioned along the double-umbrella motif.

Patent Foramen Ovale

The foramen ovale is a "flap valve" communication between the right and left atria, which in utero allows oxygenated blood from the placenta to preferentially cross over to the left side of the heart and perfuse the upper body. Shortly after birth, the pulmonary vascular resistance drops. Consequently, the left atrial pressure rises above the right atrial pressure, resulting in functional closure of the foramen ovale. In the majority of patients, this leads to fibrosis and scarring with ultimate closure of the "flap valve" communication. However, in up to 25% of the population, permanent closure does not occur, resulting in a patent foramen ovale (PFO). The presence of PFOs has been associated with "idiopathic" stroke/transient ischemic attack, migraine (particularly with aura), platypnea orthodeoxia, and decompression sickness. Despite highly publicized continued use as treatment for stroke, therapeutic closure of PFOs in patients with stroke and presumed paradoxical embolism (PPE) remains controversial because the causes and natural history of these embolic events are unclear.[83-86] The ability of clinical (multiple prior embolic events or silent events by brain scanning, occurrence with Valsalva) or echocardiographic ("large volume" right-to-left shunting, atrial septal aneurysm/hypermobile atrial septum) features to identify patients at high risk for recurrence is unknown, although several lines of evidence suggest that patients with hypermobile atrial septum may be at increased risk.[85] In an attempt to generate most meaningful data (to guide construction of sufficiently powered randomized controlled trials) from the disparate and uncontrolled nature and results of series of both medical treatments and percutaneous PFO closure, we chose to estimate the relative benefit of transcatheter device closure compared with medical therapy via systematic review and pooled analysis.[87] This suggested that approximately two thirds of recurrent thromboembolic events may be prevented by percutaneous PFO closure when compared with medical therapy, corresponding to a 4% absolute reduction in annual events. These data helped lay the foundation for the establishment of ongoing randomized controlled trials assessing the role of PFO closure in addition to short-term medical therapy versus prolonged best medical therapy as treatment for young adults with presumed paradoxical embolization via PFO.

A number of attempts at randomized controlled trials (PC Trial, PEPSI Trial) occurred throughout the past decade but failed largely due to a combined lack of (1) neurologist-cardiologist-primary physician teamwork and coordination of goal and effort; (2) modern precise definition of ischemic neurologic outcome; (3) data to generate realistic hypotheses and sample size requirements; (4) referring physician and investigator motivation to enroll all candidate patients into randomized expert care; (5) industry-based sponsorship of a sufficiently sized trial to adequately address power concerns; and (6) a "tipping point" mentality that stroke associated with PFO is a true and highly morbid disease, requiring study and relief. This milieu has radically shifted, with potential accomplishment of many, if not all, of the previously mentioned limitations, setting the stage for current, randomized, controlled comparison of percutaneous PFO closure and other therapies for persons affected by CS. The largest such trial, CLOSURE-1, is a > 1600-patient, randomized, controlled trial in > 80 participating centers (neurologist principal investigatorships), evaluating cardioSEAL-STARFlex versus tightly controlled

best medical therapy, sufficiently powered to test superiority of percutaneous PFO closure versus medical therapy in persons with imaging-confirmed index stroke, evaluating similar hard neurologic endpoints as primary outcome. A second trial, RESPECT, is a 300-patient trial comparing Amplatzer PFO Occluder PFO occlusion with clinician-determined "best medical therapy," powered to test equivalency of percutaneous PFO closure (trial estimates of < 1% endpoint occurrence) versus best medical therapy in persons with "clinically symptomatic" index stroke, evaluating similar symptomatology as primary outcome (The European "PC" trial was an early precursor to the U.S.-based RESPECT trial). The differences between the two trials (superiority versus equivalency trials, projected number of patients necessary for enrollment, definition of neurologic entry, and outcome criteria) likely belie the industry- and investigator-based differences in underlying acceptance of (1) individual series-based estimates of stroke/TIA recurrence, (2) cardiologists versus neurologists as primary assessors of cerebrovascular health, (3) standardization and precision of definition of ischemic neurologic injury, and (4) desire to be the pivotal concept trial rather than a supportive equivalent therapy.

In light of the previously mentioned trials, we strongly advocate the following measures:

- Rapid investigation of patients with cryptogenic stroke including prompt assessment for and anatomic definition of PFO. Recognition of presence of PFO requires clinician pursuit of diagnosis coupled with appropriate testing tools and technical interpretation. There is a wide range of sensitivity and specificity of currently available diagnostic tests for PFO. Although transthoracic echocardiography with Mueller maneuver (forcing right atrial pressure to bow the atrial septum leftward) may carry high sensitivity and specificity for PFO diagnosis in limited centers, only transesophageal or intracardiac echocardiography currently offer natural and anatomic detail of intracardiac shunting, though likely with lesser sensitivity in diagnosis. Therefore, although individual institutions may offer various "first-line" testing for the presence of intravascular shunting, we recommend transesophageal echocardiography for all patients with cryptogenic stroke and suspected PFO.
- Patient education regarding association of cryptogenic stroke and PFO, with emphasis on recognition of lack of randomized controlled data suggesting superiority of any particular therapy, as well as individual "risk factors" for recurrence of symptomatology. Patients should be counseled that unknown potential for systemic venous thrombosis or embolization persists after percutaneous PFO closure if anticoagulant therapy is not used.
- Removal or reduction of all potential procoagulant risks (e.g., trauma, obesity, inactivity, oral contraception, cigarette use).
- Enrollment of all eligible patients into randomized controlled trials evaluating safety and efficacy of treatment arms. Although we favor answering potential for superiority in trials on the basis of the most rigorous data analysis, both CLOSURE-1 and RESPECT remain reasonable enrollment options.
- PFO closure in patients not eligible for trial enrollment due to stroke recurrence despite compliant medical therapy (current potential after failure of warfarin use under FDA humanitarian device exemption rules for either cardioSEAL or AGA PFO occluder) or with inability to safely comply with medical therapy. Although we favor percutaneous PFO closure, surgical closure should be offered as a reasonable and accepted alternative. We are hopeful that randomized controlled assessment of percutaneous versus surgical PFO closure will occur on the basis of the results of completion of the trials noted previously.

Patent Foramen Ovale and Hypoxemia

Pressure overload of the right atrium may lead to pathologic right-to-left shunting in patients with a PFO. This may accompany chronic alteration of right-sided filling or capacitance (RV infarction, pulmonary embolism, Ebstein's anomaly) or transient decrease in RV filling seen with change from supine to an upright position (orthodeoxia-platypnea syndrome). We have closed PFOs with double-umbrella devices in more than 100 patients with RV infarction, Ebstein's anomaly, and the orthodeoxia-platypnea syndrome.[88] In all but two patients with Ebstein's anomaly, catheter closure relieved cyanosis and symptoms and eliminated the need for open-heart surgery (Fig. 42–4). The long-term benefits of PFO closure in patients with Ebstein's anomaly require further study.

Patent Foramen Ovale and Migraine

The recognition of an association between migraine syndrome with aura (M+A) and PFO appears to have come "full circle" over the past 2 decades. Initial concerns from cardiologists centered around postimplant precipitation of migrainous events "mimicking" original neurologic presentation in persons after percutaneous PFO closure. True incidence was not catalogued but was sufficient to separately raise suspicions for investigators implanting differing closure devices. Effects from general anesthesia, raised ambient catecholamines, particulate metallic embolization, and embolization of procoagulant microaggregates were all theorized as related to occurrence.

Neurologists long suspected M+A as a risk factor for stroke in the young, both from clinical and pathophysiologic concerns. Analysis of the large Lausanne stroke database highlighted the additive risk of M+A in the occurrence of ischemic stroke, particularly in the young.[89] Smaller epidemiologic studies have suggested that PFO prevalence in persons suffering M+A, regardless of occurrence of CS, was as high as that seen in young persons with CS without M+A.[90,91] Etiologic potential for right-to-left passage of as yet unclear circulating factors via PFO in patients with these syndromes requires further assessment.

Despite case series documenting PFO closure effects in persons with M+A,[92,93] given the competing concerns of both precipitation and reduction of M+A in persons with and without prior M+A receiving therapy for PFO, there is little reason, at the present, to expect a given clinical outcome from any specific treatment. Although improved basic etiologic and epidemiologic study of this phenomenon is required, as well as study of the effects of various antiplatelet and anticoagulant postimplant "protective" regimens currently employed, randomized placebo (sham procedure) controlled trials comparing PFO closure with cardioSEAL-STARFlex + short-term antiplatelet therapy versus best medical antimigraine therapy in patients with resistant migrainous symp-

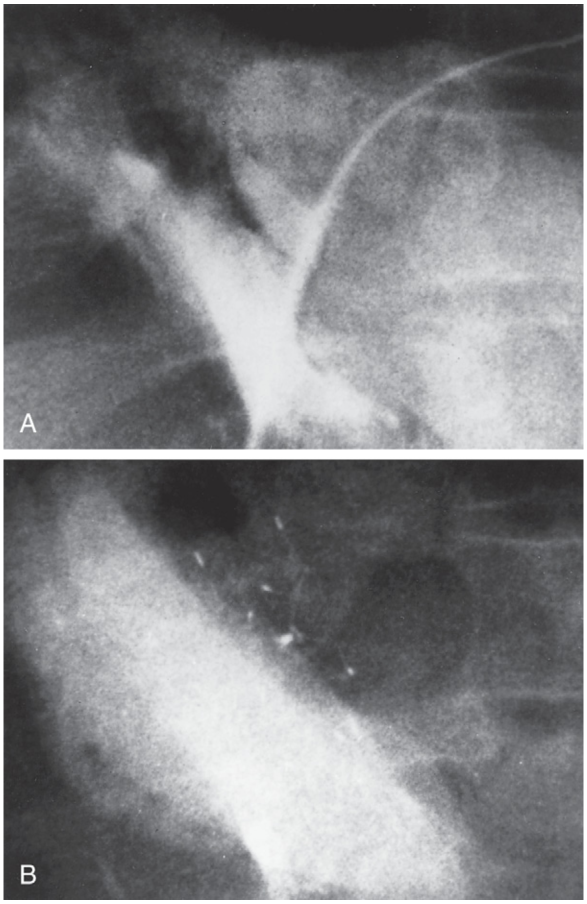


Figure 42–4 Intracardiac passage of contrast across the foramen ovale, from right atrium to left, via a patent foramen ovale (PFO), is noted in this patient with orthodeoxia-platypnea syndrome. Camera is situated left anterior oblique with cranial angulation, with patient laying supine, head towards the top of the page. In **(A)** a wire is seen extending vertically from the bottom (IVC) of the angiogram passing through the right atrium, the atrial septum, the left atrium, and extending to the left upper pulmonary vein (*top right corner*). The patient, status post thoracotomy, was unable to work, given resting aortic oxygen saturation: supine 100%, standing 82%. A clamshell occluder was implanted on the atrial septum, closing the PFO. In a right atrial angiogram **(B)** in similar projection, radiopaque markers highlight the distal most ends of each of the device arms (2 superior arm markers are seen on each side of the septum, with only one inferior left atrial marker visible in this projection), with a more prominent central opacity in the device hub, where all 8 of the arms connect together. Contrast flow is limited by effective PFO closure to the angiographically inferior and leftwardly projected right atrium. After PFO closure, the patient returned to work with finger oximetry: supine 100%, standing 100%.

toms, are completed and awaiting analysis in the United Kingdom (MIST I, and are under way in the United States with both the cardioSEAL-STARFlex, as well as the Premere (St Jude Medical, Inc., St. Paul, Minn) PFO closure system (MIST II and ESCAPE trials, respectively). We do not recommend PFO closure at the present for persons with M+A without CS, though we strongly support further study, within the context of these trials.

Recommendations

The decision to close PFOs associated with presumed paradoxical embolization is complicated by the high frequency of PFOs in the normal population (25%) and the common occurrence of idiopathic strokes in adult populations. Only randomized prospective trials will successfully address these issues. At present, transcatheter PFO closure is recommended for (1) patients with recurrent neurologic events despite compliant medical therapy (Coumadin) or patients with an absolute contraindication to anticoagulation, (2) PFO associated with platypnea orthodeoxia (see Fig. 42–4), or (3) within the constraints of randomized controlled study for control of cryptogenic stroke or refractory migraine.

Biscuspid Aortic Valve

Bicuspid aortic valve is the most common congenital heart defect in the older population, found in 1% to 2% of adults (older than the age of 18 years), and may be associated with other left-sided obstructive lesions, such as aortic coarctation. Progressive pathological dilation of the aortic root, with or without dissection, may be seen even in the absence of obstructive gradient or regurgitation. Stenosis of the bicuspid valve is associated with (though not dependent on) increasing age and presence of fibrocalcific disease. Aortic insufficiency occurs in younger patients and may be an isolated hemodynamic lesion, due to endocarditis or cystic medial necrosis/aortic root dilation. Endocarditis prophylaxis is recommended for all adults with bicuspid aortic valves.

Although the First and Second Natural History of Congenital Heart Defects Studies outlined the course and treatment of bicuspid aortic valve disease primarily in infants and children, the natural history of bicuspid aortic valve disease and criteria for intervention in the older patient are less well defined.[94,95] Sudden death in the occasional asymptomatic patient with apparent preserved ventricular function and only moderate obstructive gradient suggests inability to extrapolate from natural history and intervention studies derived from adults with acquired calcific stenosis.

Surgical aortic valve replacement is the treatment of choice when aortic root surgery is required. Preference for the more detailed pulmonary autograft to the aortic position and subsequent homograft implantation into the pulmonary position ("Ross" procedure) compared with "standard" homograft, tissue, or prosthetic valve alternatives has fallen out of favor. Excellent results can be obtained with all the approaches noted earlier, although each procedure carries its own immediate and long-term complications.

The acceptance of balloon aortic valvuloplasty (BAV) as palliation for children with bicuspid aortic stenosis is in contradistinction to the treatment of elderly patients with calcific AS. Two reports have underscored the utility of BAV in selected young and intermediate-aged adults with noncalcified stenotic aortic valves.[96,97] Patients with increased valvular calcification demonstrated a trend toward higher gradients both before and after BAV and decreased incident-free survival compared with patients without calcified valves. Balloon-mediated worsening of aortic regurgitation, a rare adverse

sequelae of BAV, did not preclude potential for subsequent successful surgical valvuloplasty.

Recommendations

The previously mentioned findings support BAV for non-calcified congenital bicuspid aortic stenosis in young- and intermediate-aged adults. This procedure can provide effective palliation and prolong the interval to surgical intervention without significantly increasing cardiac morbidity or serious complications. Immediate recognition of the uncommon complication of balloon-induced avulsion of a valvular cusp during BAV allows effective and timely surgical therapy. Surgical options remain acceptable for the symptomatic patient with calcific disease, noncalcific disease associated with enlarged aortic root (>4.5 cm) or greater than or equal to moderate valvar regurgitation. We recommend an attempt at balloon valvuloplasty for symptomatic patients 40 years old and younger with at most a mildly calcified bicuspid aortic valve, gradient ≥ 60 mm Hg with preserved ventricular function, or gradient < 60 mm Hg with associated ventricular dysfunction. Despite treatment of valvular disease, vigilant lifelong assessment of the ascending aortic health is warranted.

Pulmonary Stenosis

Pulmonary stenosis (most commonly valvar, although branch pulmonary artery and subvalvular obstruction can occur as well) occurs in > 10% of patients with congenital heart disease. Adult presentations may range from no symptomatology to profound fatigue and dyspnea, depending on the degree of stenosis and RV impairment.

The First and Second Natural History of Congenital Heart Disease Studies led to classification of degree of stenosis as mild (RV systolic pressure ≤ 50 mm Hg), moderate (RV systolic pressure 50 to 100 mm Hg), or severe (RV pressure > 100 mm Hg).[98] Given the unclear natural history of valvar pulmonary stenosis in adults, criteria for timing and nature of intervention has become dependent in large part on development of symptomatology, extrapolation from the natural history in children, and decreasing risk of interventions.

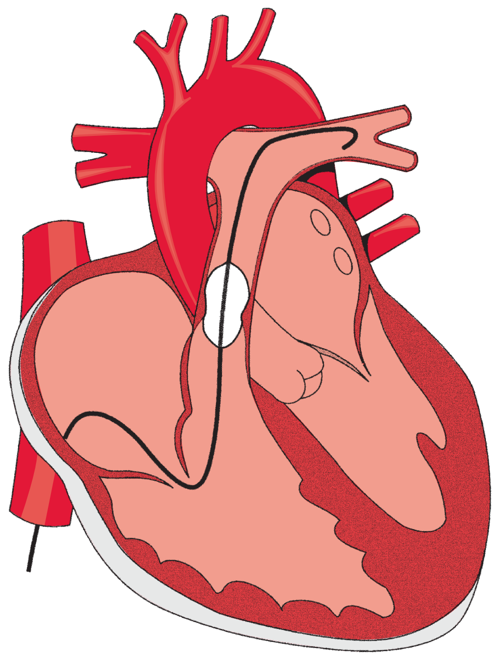


Figure 42–5 The technique of balloon pulmonary valvuloplasty.

Although open surgical valvotomy was historically the initial therapeutic approach, the present treatment of choice for patients with nondysplastic valvar pulmonary stenosis is balloon pulmonary valvuloplasty (Fig. 42–5). Numerous single-center reports (each with 4 to 53 patients) have demonstrated similar immediate gradient reduction with BPV in young and middle-aged adults, aged 13 to 55 years, using standard single, Inoue, or double balloon techniques to achieve a balloon-to-annulus ratio between 1.1 and 1.4.[99] The mean follow-up in these series ranged from 0.5 to 6.9 years and, when compared with results in pediatric-aged individuals, revealed a decreased incidence of periprocedural morbidity and restenosis in the adult. Hemodynamically compromising or therapy-requiring infundibular spasm is uncommon and has not been seen in either our experience or in the largest reported series, although individual instances of surgically treated pericardial tamponade, severe infundibular obstruction, periprocedural sepsis, and postprocedural diffuse pulmonary edema have been reported. Brief inflations with rapidly deflating balloons allow avoidance of prolonged reductions in cardiac output in the elderly or those with low output at baseline. Pulmonary regurgitation after BPV is usually mild, though single-center study suggests high potential (40% of cohort) for surgical valve intervention at late (30-year) follow-up.[100]

Recommendations

Given the low attendant morbidity of BPV, we perform this procedure for any adult patient with gradient > 40 mm Hg and normal RV function (lower gradient if cardiac output is reduced, RV systolic function appears subnormal or RV end diastolic pressure is > 12 mm Hg) either in the individual with unoperated valvar PS or with recurrent VPS after initial surgical treatment. Long-term follow-up for potential effects of pulmonary regurgitation on RV function is warranted.

Aortic Coarctation

Aortic coarctation (CoA), typically a narrowing of the descending aorta at the site of insertion of the ductus arteriosus, distal to the origin of the left subclavian artery, occurs in 5% to 10% of patients with congenital heart disease. An accompanying bicuspid aortic valve is present in 40% to 80% of patients with CoA.

Clinically detectable CoA in the adult, with a resting gradient ≥ 20 mm Hg between upper and lower extremities, carries an increasing risk of progressive left ventricular dysfunction, persistent systemic arteriolar systolic hypertension, premature cerebrovascular and coronary atherosclerosis, and the potential for dissection or rupture of the aorta and coronary or cerebral vessels (especially during pregnancy, surgery, or catheterization) (Fig. 42–6). Diagnostic modalities employed to confirm the diagnosis of aortic coarctation and further delineate precise anatomic detail, the presence of cerebral vascular anomalies, and the presence of LV hypertrophy are echocardiography and MRI.

Because of a combination of amplification of the gradient wave, as well as stress on the myocardium and vasculature at all portions of ejection phase in the cardiac cycle (ventricular-arterial coupling), the effects of seemingly “mild” gradients across CoA may be profound. We consider indications for repair to be (1) the presence of a resting gradient ≥ 20 to 25 mm Hg with normal LV function, (2) less gradient with accompanying abnormal LV function, or (3) systemic hypertension that requires more than “simple” therapy to achieve normotension. Surgical end-to-end, or bypass, repair has previously been the standard approach, with excellent results and perioperative mortality of ≤ 2% for native CoA repair. Perioperative concerns of low, but present, risk of spinal cord ischemia or bleeding from collateral vessels are amplified in the patient with recurrent stenosis after initial repair. Late postoperative complications including the development of aortic aneurysms and recurrent coarctation have been reported in up to 20% of patients undergoing surgical repair, although the surgical risk of mortality at reoperation, paraplegia, and late aneurysm formation has been estimated at ≤ 2% at appropriate centers. A high incidence of late postoperative recurrence of systemic hypertension, inversely correlated with age at repair, has been noted. Patients must be screened on a continuous basis for sequelae of aortic and systemic capacitance vessel noncompliance, aneurysms of the cerebral vasculature,[101] aortic dissection, and premature coronary atherosclerosis. We recommend that patients be examined yearly with particular emphasis on symptoms suggesting lower extremity or coronary ischemia or cerebral aneurysm. In addition, we suggest noninvasive imaging with MRI every 3 to 5 years (more frequently if aneurysm or restenosis is present) and exercise testing as suggested by history and examination.

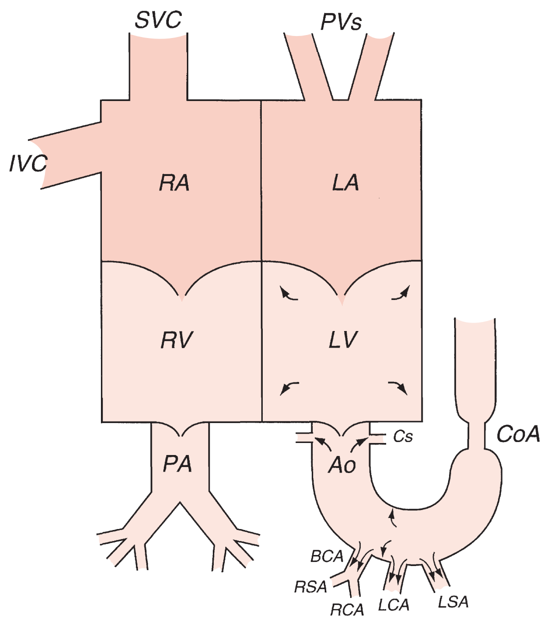


Figure 42–6 Aortic coarctation physiology. Narrowing in the descending aorta, just distal to the origin of the left subclavian artery. Wall stress is raised in all proximal chambers and vessels, leading to potential for advanced atherosclerosis, vascular dissection or rupture, and chamber hypertrophy. BCA, brachiocephalic artery; CoA, aortic coarctation; LCA, left carotid artery; LSA, left subclavian artery; RCA, right carotid artery; RSA, right subclavian artery.

In children and adults, balloon dilation or stenting of recurrent, or persistent, CoA following surgical correction is now considered the therapy of choice. Moreover, balloon dilation or stenting is also considered an effective alternative to surgical correction as therapy for native CoA, with up to 15-year follow-up reported at some centers.[102-109] Success (defined either as gradient reduction of ≥ 50% and an increase in angiographic luminal diameter ≥ 30% or, more recently, as a residual gradient ≤ 20 mm Hg with near universal reduction in antihypertensive therapy) is high (>80%) and morbidity is low using balloons chosen to be 3 to 4 times the diameter of CoA and not more than 150% the transverse arch diameter. Estimates of complications include procedure-related death in 0.7%, periprocedural stroke in 0.6%, transmural (0.7%) or intimal dissection (1.6%) with rare need for surgical intervention, and postprocedural aneurysm (7% to 12%). Risk of complication may be increased with increasing age and in the presence of concomitant bicuspid aortic valvular disease.[110] Balloon-assisted stenting of the aorta (Fig. 42–7) without prior maximal balloon dilation permits use of smaller, non-“oversized” balloons, theoretically with less risk of dissection and rupture of the aortic wall.[111] Care should be taken to avoid extrapolation of results obtained with similar techniques in children to the adult population, especially given the potential for increased changes in capacitance, compliance, and atherosclerosis in the walls of conduit arterial vessels proximal to the CoA. The relative safety of surgical versus transcatheter balloon/stenting repair of CoA in adults who may wish to face future pregnancies or sustain significant physical exertion remains to be clarified. Standardization of indication, procedural technique, follow-up, and outcomes assessment remains the major limitation of most studies. The usefulness of surgery versus endovascular transcatheter therapies, when concomitant aortic dilation or aneurysm is present, remains undefined. We await results of newly formed interventional registries, as well as studies assessing ventricular-arterial coupling,[112-114] to better assess safety and efficacy of catheter-based and surgical therapies.

Recommendations

We recommend balloon-assisted stent implantation, or balloon dilation alone, as effective alternative therapy for all adults with native or recurrent CoA and > 20 mm Hg gradient, or < 20 mm Hg gradient with decreased LV function or symptoms of LV failure, coronary ischemia, or lower extremity claudication. Definition of indication and technique for catheter-based, as well as surgical intervention based on natural outcomes in the modern era, coupled with standardized long-term follow-up, is eagerly awaited. We consider long-term annual interviews and examinations coupled with noninvasive imaging at intervals ≤ every 3 to 5 years to assess systemic arterial and left ventricular sequelae after CoA repair to be essential. Optimal management of the patient with aortic coarctation with associated aortic dilation remains undefined.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cyanotic congenital lesion that allows survival into adulthood, with approximately 2000 new persons reaching adulthood with TOF each year in the United States. Modern understanding of

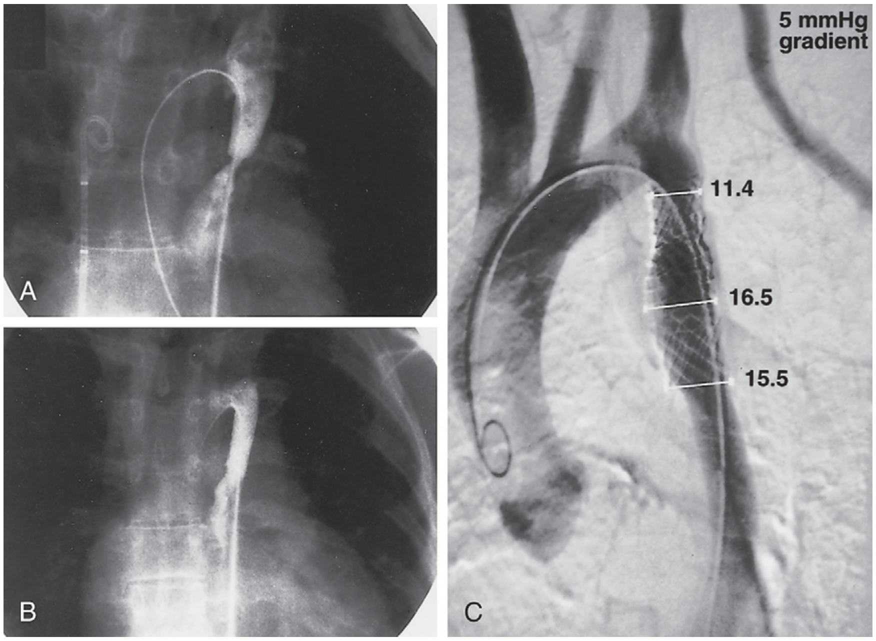


Figure 42–7 **A,** Unrecognized coarctation of the aorta (80 mm peak systolic gradient) leading to left heart failure and premature atherosclerosis of the coronary and cerebral arterial vasculature. Initial balloon dilation and stent implantation, with small distal dissection (**B**), later covered with a second stent (**C**). A residual gradient across the entire segment of < 5 mm Hg was noted.

TOF considers this lesion to more appropriately be classified as "monology" (i.e., caused by a single unifying abnormality, namely hypoplasia and displacement of the conal, or infundibular, septum). This anterior and superior displacement results in obstruction of the RV outflow tract (pulmonary stenosis) with resultant RV hypertrophy, leaving behind a ventricular septal defect in the conal septum (Fig. 42–8). The aortic annulus is intimately opposed to the conal septum, and displacement of one leads to opposing displacement of the other (i.e., posterior inferior displacement of the aortic annulus taking a position overriding the ventricular septum).

The degree of hypoplasia and septal malalignment determines the severity of encroachment into the RV outflow tract (although always associated with a large conoventricular VSD) with clinical presentations ranging from (1) minimal RV outflow obstruction ("pink" TOF) with predominant left-to-right shunting; (2) moderate RV outflow obstruction (most common), with bidirectional shunting and cyanosis; and (3) severe forms of RV outflow obstruction (pulmonary atresia) in which cyanosis is obligatory and pulmonary artery flow arises from persistent primitive aorta-pulmonary artery collaterals.

In patients with TOF/pulmonary atresia, aorta-pulmonary artery collateral vessels make up many/all of the various subdivisions of the lung vascular tree, ranging from the main or central pulmonary arteries (which may be absent) to individual/multiple proximal branch pulmonary arteries, to subsegments of lung vasculature. These collaterals frequently have failed involution, have retained stenoses and abnormal vascular walls, and may undersupply or oversupply particular lung segments.

Although TOF is typically diagnosed and repaired in childhood, presentation during adult years can occur in patients who have previously undergone palliative operations, as well as in those without prior operations. In the past, before development of a successful complete repair strategy, patients were managed with systemic-pulmonary arterial shunts (central Waterston, Potts, and classic/modified Blalock-Taussig shunts; also see Table 42–1). Residual postoperative shunt complications include pulmonary artery distortion or pulmonary vascular disease/hypertension, and peripheral pulmonary artery stenoses. Complete repair of TOF includes obliteration of any preexisting shunts, elimination of RV outflow obstruction (with or without transpulmonary annular incision and patching), and VSD closure. Additional residual postoperative lesions may include residual VSD, RV outflow obstruction, and pulmonary regurgitation.

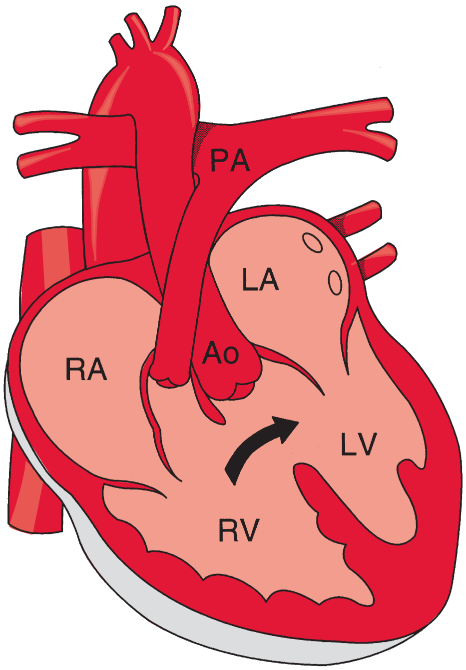


Figure 42–8 Tetralogy of Fallot.

Data regarding long-term follow-up of repaired TOF reveal excellent long-term survival after the initial operative period, with 32-year survival of 86% compared with 96% in a control-matched population, and appear most favorable when (1) VSD is closed, (2) RVOT obstruction is near completely relieved, and (3) severe PR and RV dysfunction is not present.[115] Multicenter data have suggested 35-year survival > 90%.[116] Although the majority of patients have excellent

Table 42–2 Causes of Ventricular Failure Following Surgical Repair of Tetralogy of Fallot

Left-Sided Heart Failure	Right-Sided Heart Failure
• Residual Ao-PA communication shunt collateral • Residual VSD patch margin native • Aortic insufficiency • Arrhythmias • Coronary artery anomaly ligation • Myocardial preservation	• RV outflow obstruction valvar supravalvar/peripheral PS pulmonary vascular disease • Pulmonary regurgitation • Tricuspid regurgitation • Atrial septal defect • Arrhythmias • Left-sided heart failure • Myocardial preservation

Ao, aorta; PA, pulmonary artery; PS, pulmonary stenosis; RV, right ventricular; VSD, ventricular septal defect.

functional capacity, some patients experience exercise limitation, right or left ventricular failure (Table 42–2), RV outflow obstruction or aneurysms (<29%), arrhythmia (<33%), and sudden death (1% to 3%).[117] Although promising, data regarding surgical repair of tetralogy for neonates and young infants are insufficient to assess long-term outcomes.[118,119]

Implicated risk factors for death after TOF repair have most commonly been sought as risks for sudden cardiac death, with little discrimination between worsened functional status and cardiac muscle dysfunction leading to premature death versus presumed arrhythmic death. These risks have been mostly defined in single-center cohort studies, with more robust data from multicenter combined assessments.[118,120] Of note, most series have not considered immediate surgical risk in such assessments (see later) and have excluded either immediate or first-year nonsurvivors, who frequently comprise a substantial population (some series up to 10% to 30%).[115,121] Single-center cohorts have continued to suggest older age at repair, prior presence or absence of palliative shunts, radiographic cardiothoracic ratio, presence of RV outflow tract patch, increased RV systolic pressure, and LV dysfunction as makers for poor outcome, in addition to pure electrical markers. Multicenter trials have emphasized older age at repair and presence of pulmonary regurgitation,[116] as well as older patient age, presence of prior palliative surgery, and increased radiographic cardiothoracic ratio as independent risks for poor outcome,[118] in addition to specific additional markers of electrical instability.

Increasing time from surgery, in and of itself, has been postulated as changing the risk of death post TOF repair, with single-center cohort data confirming risk of sudden death increasing from 1.2%, 2.2%, 4%, and 6% at 10, 20, 25, and 35 years after operative repair, with mortality risk of 0.27%/year until 25 years after surgical correction and 0.94%/year thereafter.[121]

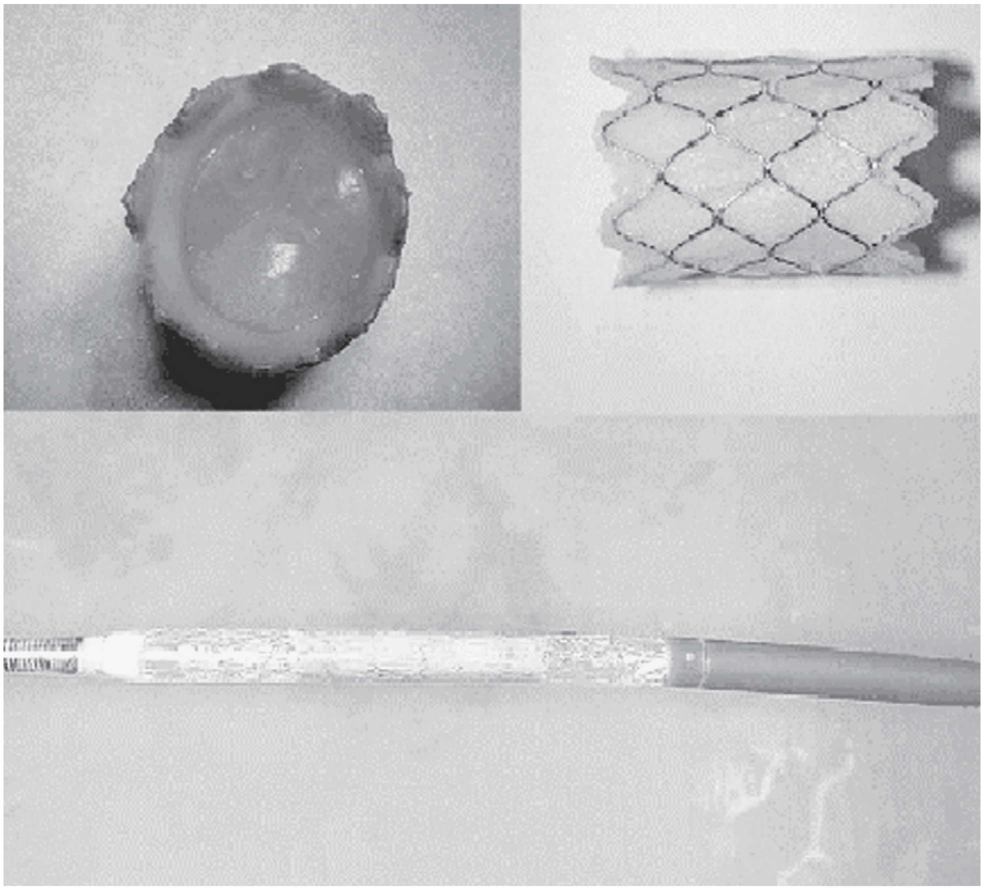
Risks for worsened functional capacity after surgical repair of tetralogy have been studied in a more modern era, using NYHA functional status (with its subjective limitations) as a standard of functional ability. RV outflow patch, as well as transannular patch repair, had similar risks for worsened functional ability, as well as for cardiac death, in single-center cohort assessment.[1] A single-center cohort study using MRI measures of RV and LV function suggests not only older age at repair, but lower LVEF and RVEF (correlating with each other, as well), as markers for worsened clinical status by NYHA functional class,[122] confirming older reports of the importance of LV function in patients with tetralogy.[123-125] Of note, in this single-center study,[126] PR fraction and RV diastolic dimensions did not independently correlate with functional status. Similar findings raising questions regarding the negative predictive potential of PR fraction include additional single-center cohorts emphasizing presence of RV outflow aneurysm or akinesia as an independent risk for worsened function (rather than PR fraction),[127] as well as lack of RV functional improvement in single-center reports after surgical PV replacement for pulmonary regurgitation in patients with tetralogy.[128,129]

Atrial arrhythmias including sinus node dysfunction, atrial flutter, and atrial fibrillation have been noted in up to one third of repaired patients and correlate with the presence of old scar or hemodynamic abnormalities. Acute intervention is frequently recommended, especially with associated ventricular or atrial dysfunction. Control of frequently recurring or incessant atrial flutter may be equally effective with radiofrequency ablation compared with the most effective medical therapy, and strategies are frequently combined. Late-onset complete heart block has been diagnosed with an incidence of 4% after a mean follow-up of 20 years.[130] The strongest risk factor for the development of complete heart block is the presence of perioperative complete heart block at the time of surgical repair.

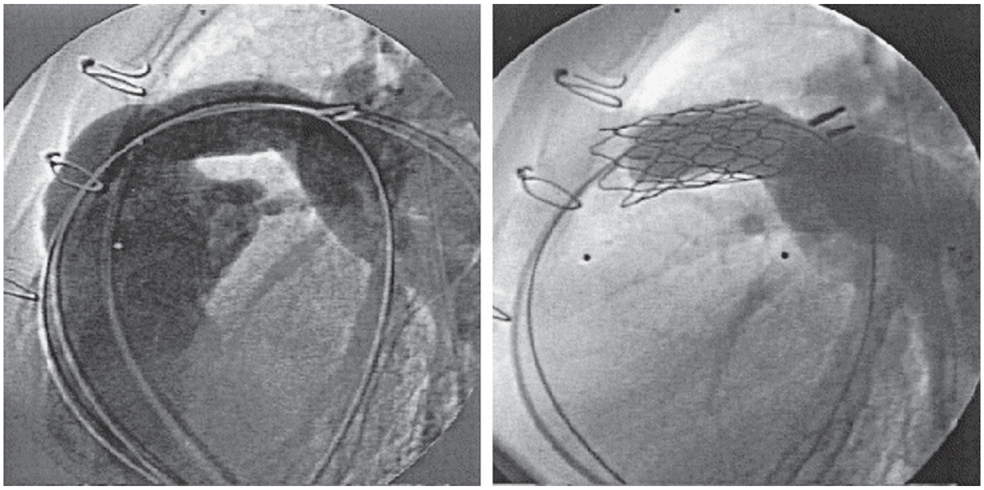
Although pulmonary valve replacement has been proposed as a treatment option for symptomatic patients, several investigators noted that placing a pulmonary valve in patients with severe RV dilatation and dysfunction may not lead to adequate functional recovery of the RV.[131-133] These observations have led several centers to advocate pulmonary valve replacement before the onset of symptoms in order to preserve RV mechanics.[131,134,135] Uncertainty regarding the optimal timing of intervention continues. Although PR is the primary source of chronic RV volume overload in these patients and correlates closely with RV size, major adverse clinical outcomes in adults with TOF and PR including death, high-grade ventricular arrhythmia, and heart failure relate primarily to effects of PR on the RV myocardium-dilatation and dysfunction, as measured by end diastolic volume Z scores and increasing myocardial fibrosis.[136,137] Until these predictors are better defined, we currently recommend following all patients with TOF and pulmonary regurgitation with serial MRI (RV forward and regurgitant volumes, ventricular function and scarring, and presence of additional anatomic abnormalities) combined with assessment of functional capacity (cardiopulmonary metabolic exercise testing) and electrocardiographic and rhythm parameters, to assist in the accumulation of sufficient potential predictive data.

An investigational percutaneous pulmonary valve has been developed, using bioprosthetic valve leaflets (bovine jugular vein) mounted on a balloon expandable stent (Fig. 42–9).[138,139] Initial procedures have been conducted within regurgitant tube conduits with relatively definable diameters, although eventual extrapolation of technique to larger and less definable outflow positions is expected.

After surgical repair of TOF, patients may have a ≤ 25% incidence of recurrence or residual obstruction at any level of



A



B

Figure 42–9 Percutaneous pulmonary valve stent implantation. **A,** De novo bovine jugular vein valve sutured within stented framework and on delivery balloon, when implanted. **B,** results in no pulmonary regurgitation on angiography. Bottom **(B)** left angiogram taken in a lateral position with patient's head toward the top of the page, notes sternal wires in vertical positioning on the left. Wires extend from the inferior vena cava (off the bottom of the page) to the right atrium and ventricle (vertically along the left side of angiogram), through the pulmonary valve and main pulmonary artery (superior horizontal coursing), extending to the more distal pulmonary arteries (vertically along the right side of the angiogram). In systole (bottom left angiogram), contrast fills the right ventricle, right ventricular outflow and main pulmonary artery and distal pulmonary arteries. The struts of the stented valve implant are minimally visible in the pulmonary valve position (superior horizontal portion). The stented valve must be in the open position, allowing passage of blood and contrast to the distal pulmonary vasculature. In the bottom rightward angiogram, taken in simlar angulation in diastole, contrast does not regurgitate back to the right ventricle after passage to the pulmonary arteries. The struts of the stented valve are well visualized. (Modified from Bonhoeffer P, Boudjemline Y, Saliba Z, et al: Percutaneous replacement of pulmonary valve in a right ventricle to pulmonary artery prosthetic conduit with valve dysfunction. Lancet 2000;356:1403-5; and Bonhoeffer P, Boudjemline Y, Qureshi SA, et al: Percutaneous insertion of the pulmonary valve. J Am Coll Cardiol 2002;39:1664-9.)

the RV outflow. In adults, use of balloon dilation and balloon-assisted stent implantation as primary therapy for native and postoperative narrowings in the RV outflow (with or without conduit/homograft placement), as well as in the proximal and distal pulmonary vasculature, have success rates similar to those observed in children. Pulmonary artery dilations are the most commonly performed interventional procedures in our catheterization laboratory (Fig. 42–10). A strategy combining dilations with low- or high-pressure balloons may achieve up to 75% procedural success in relief of obstruction in peripheral pulmonary arteries (defined either as an increase of ≥ 50% of predilation vessel diameter, an increase of > 20% of flow to the affected lung, or a decrease of > 20% in systolic RV-to-aortic pressure ratio).[140] Dilation of vessels that exhibit kinking or significant recoil (proximal branch PAs) can be improved with placement of intraluminal stents, achieving a > 90% initial procedural success rate.[141] Stent implantation within stenotic valved homografts or conduits must be tempered by the potential for an increase in pulmonary valvar insufficiency. Complications of conduit/vessel rupture, aneurysm formation, or development of high-flow reperfusion edema may occur and infrequently (each < 1% incidence) have been correlated with oversizing balloons (especially in calcified conduits or homografts) and with postprocedural mean PA pressures ≥ 40 mm Hg. Balloon dilation or stent implantation remains the procedure of choice for such patients when additional surgery is not required and when obstruction is at the level of the pulmonary trunk or beyond.

We have extended these dilation techniques to adult patients with either isolated peripheral pulmonary artery stenoses or acquired chronic distal thromboembolic pulmonary hypertension (Fig. 42–11).[142] Most were profoundly debilitated and were referred for evaluation for lung transplantation. The most frequently encountered complication was early development of transient reperfusion pulmonary edema in segments of lung with restored pulmonary blood flow after dilation. After 3 to 4 years of follow-up, survivors have improvement in exercise tolerance.

Embolization coils (see PDA), vascular occlusion devices, and covered stents have been used in adults with TOF to eliminate both residual central aorta or systemic artery to pulmonary artery shunts, as well as duplicate aorta to pulmonary artery collateral vessels.

Recommendations

The adult with repaired TOF faces excellent chances of prolonged survival. Long-term risks include development of (1) RV central or peripheral outflow obstruction, (2) pulmonary regurgitation, (3) RV dilatation and scarring, (4) residual shunting at the septal, aorta-pulmonary shunt or collateral level, (5) conduction disease with potential heart block, (6) atrial arrhythmias, (7) ventricular arrhythmias, and (8) sudden death. Patients should undergo annual interview and physical examination, pulse oximetry, and ECG. We recommend 24-hour ambulatory ECG monitoring every 2 to 3 years and either echocardiography or MRI every 3 to 5 years, more frequently if anatomic, arrhythmic, or functional abnormality is documented. Exercise and metabolic cart cardiopulmonary testing should be performed every 3 to 5 years. We consider balloon dilation or stent implantation to be the procedure of choice for relief of outflow obstruction and transcatheter embolization to be the procedure of choice for elimination of residual shunting/extraneous vessels when additional surgery is not required. The role of percutaneous pulmonary valve implantation as compared with surgical valve replacement and RV remodeling remains undefined. Although electrophysiologic study (EPS) may highlight highest-risk populations for sudden cardiac death (SCD), widespread application of EPS to the total adult TOF population remains impractical given the relatively low overall SCD rate. Aside from the group of TOF adults experiencing aborted SCD, there remains little consensus regarding other subsets of patients with TOF for whom benefit would exist with prophylactic implantation of ICD.

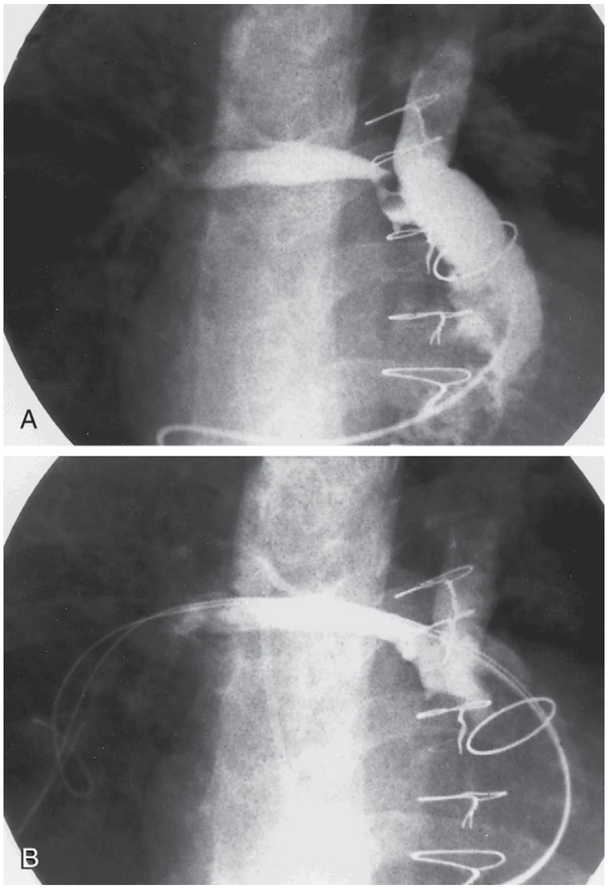


Figure 42–10 High-pressure balloon dilation of postoperative proximal RPA stenosis (**A**) leads to elimination of gradient, increased angiographic vessel caliber (**B**), and resolution of flow imbalance by nuclear lung scintigraphy. In **(A),** catheters and wires are placed via the IVC (off the bottom of the angiograms) through the right atrium (from leftward and inferior) through the right ventricle (vertically and superior) and right ventricular outflow to the distal pulmonary arteries. Contrast fills the main and proximal branch pulmonary arteries. At the junction of the sternal wires and the horizontally imaged right pulmonary artery, lack of opacification represents postoperative proximal right pulmonary artery stenosis in this patient. High pressure balloon dilation was performed, and the proximal branch pulmonary arteries are reimaged **(B),** showing resolution of the stenosis, with continuity of contrast opacification. The gradient was eliminated and vessel caliber was increased.

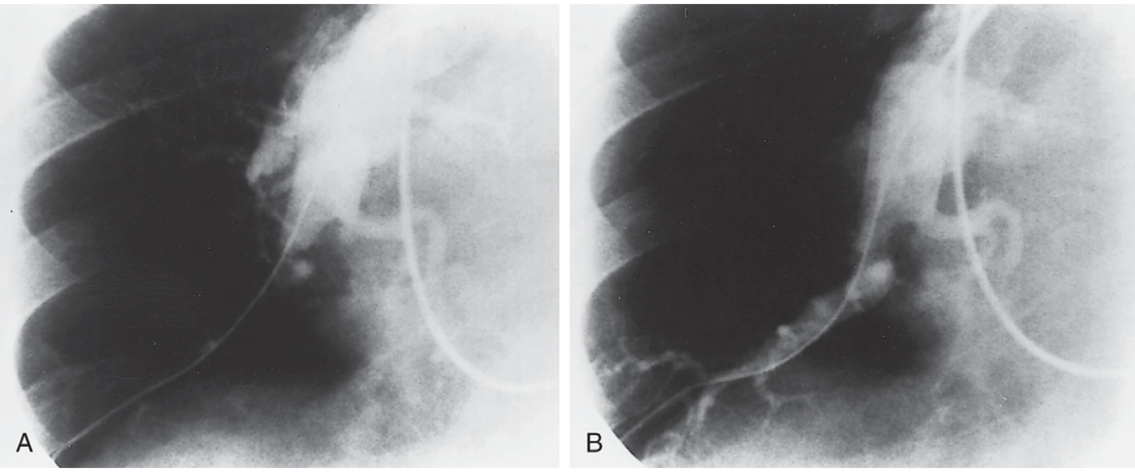


Figure 42–11 Right lower lobe segmental vessel before (**A**) and after (**B**) 7-mm balloon dilation. Mean central PA pressure fell from 60 mm Hg to 40 mm Hg. Reperfusion pulmonary edema was recognized 15 minutes after dilation.

Patent Ductus Arteriosus

The ductus arteriosus remains patent in approximately 0.07% of live births (5% to 10% of all congenital heart disease), connecting the descending aorta and the junction of the main and left pulmonary arteries. Anatomically, it varies in size and shape and may be calcified or aneurysmal. Difference in relative vascular resistance and physical restriction of the ductus determine the degree and nature of intravascular shunting (typically left to right) (Fig. 42–12). Patent ductus arteriosus in the adult is usually asymptomatic, although it may produce symptoms caused by increased volume load on the left ventricle. The diagnosis should be suspected in the setting of a continuous murmur at the left upper sternal-subclavicular border.

Endocarditis remains a constant risk (≈0.5% to 1.0% per year), although this is debated in the modern antibiotic SBE prophylaxis era. The risk of developing left ventricular dysfunction increases with age. Although operative closure in infancy is both safe and relatively straightforward, surgical repair requires general anesthesia, thoracotomy, and postoperative recuperation. In adults, surgical closure may be more complicated due to anatomic features of the patent ductus (calcification, friability, and aneurysmal dilatation), as well as increased incidence of multiple organ system comorbidity.

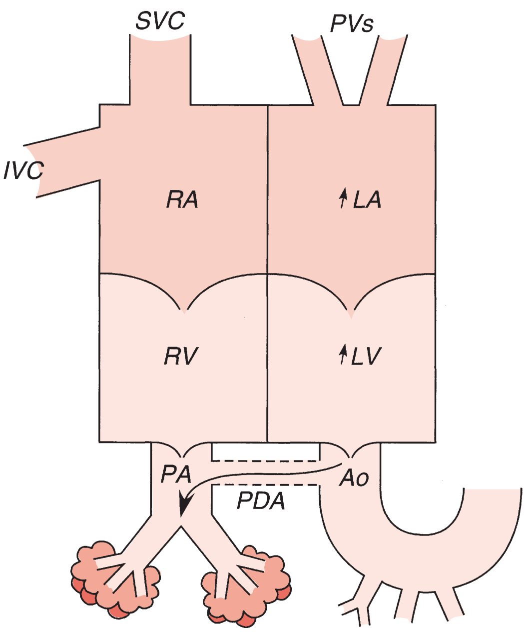


Figure 42–12 PDA physiology. Intravascular shunting is governed by relative resistance of pulmonary versus systemic arterial bed. Unless pulmonary vascular disease exists, flow is left to right with enlargement of left-sided chambers.

A transarterial transcatheter device approach to PDA closure was devised by Porstmann and colleagues.[143] Today, the most common devices used for transcatheter PDA occlusion are the Amplatzer PDA Occluder device and embolization coils, with nearly universal success at closure of PDA with one device or another.[144,145] The inexpensive cost along with the ease and effectiveness of occlusion make the embolization coils the ideal device for closure of PDAs.[146-149] We tend to use coils (single versus multiple, standard, controlled delivery, or shaped) for PDAs that have a minimal diameter < 3 to 4 mm and Amplatzer PDA Occluders for PDAs that have a minimal diameter ≥ 4 mm.

In our clinical service, we close all audible PDAs via a transcatheter approach. Patients do not leave the catheterization laboratory with evidence of residual ductal flow. Post device closure, bacterial endocarditis precautions are maintained for 6 months.

Recommendations

Despite unclear risks of bacterial endocarditis in the current antimicrobial era, we recommend transcatheter PDA occlusion as the procedure of choice for adults with audible PDA and PDA associated with left ventricular dysfunction. Coil embolization is the device of choice, with the use of alternative occlusion devices such as the Amplatzer device for PDAs with a minimal lumen diameter of ≥ 3 to 4 mm.

Ventricular Septal Defects

Isolated ventricular septal defects are the most common congenital defect seen in childhood, although they are much less frequently encountered in adult life due to either spontaneous or surgical closure during infancy or childhood. Anatomical classification is based on septal location including perimembranous, subpulmonary, AV canal-type, and muscular. Nature

and degree of intracardiac shunting depend on the relative pressure difference, ventricular chamber compliance and capacitance, and anatomic restriction of the VSD (Fig. 42–13). VSD closure is recommended for relief of symptoms (dyspnea, exercise incapacity) when accompanied by excessive pulmonary blood flow (typically with pulmonary/systemic blood flow ratio > 1.5 to 2.0) and left ventricular volume loading, in the absence of excessive pulmonary vascular resistance (typically < 7 to 8 Wood units·meter^2 or 280 to 430 dynes-sec·cm^{-5}) without reactivity to pulmonary vasodilators). We also consider closing VSDs with a pulmonary/systemic flow ratio < 1.5 to 2 if left ventricular failure is present. Spontaneous closure of tiny or small defects has been reported even into adulthood. We recommend that adults with persistent, nonhemodynamically significant VSDs have an interview and physical examination every 2 years with echocardiography every 3 years to screen for development of aortic regurgitation, arrhythmia, and potential for SBE. Excessive flow and pressure entering the pulmonary vasculature may contribute as an additional "trigger" to the development of pulmonary vascular hypertension and potential for shunt reversal, cyanosis, and the sequelae of Eisenmenger's disease.

We have applied transcatheter closure techniques for the treatment of congenital, postoperative residual, and acquired forms of VSDs using FDA-approved double umbrella devices in an attempt to eliminate the need for, or reduce the risk and complexity of, surgical repair.[76,150,152] To date, the majority of closures have been in patients with muscular VSDs

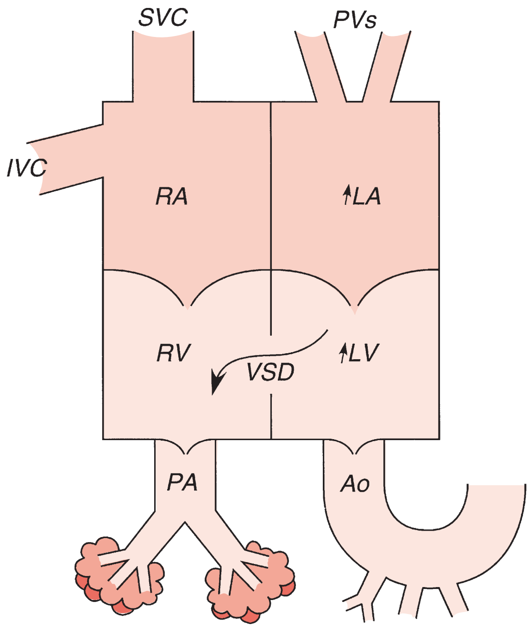


Figure 42–13 VSD physiology. Intracardiac shunting is governed by relative resistance to ventricular contraction and less so by ventricular filling. Unless RV function is significantly compromised or severe pulmonary hypertension/vascular disease exists, flow is left to right with enlargement of left-sided chambers.

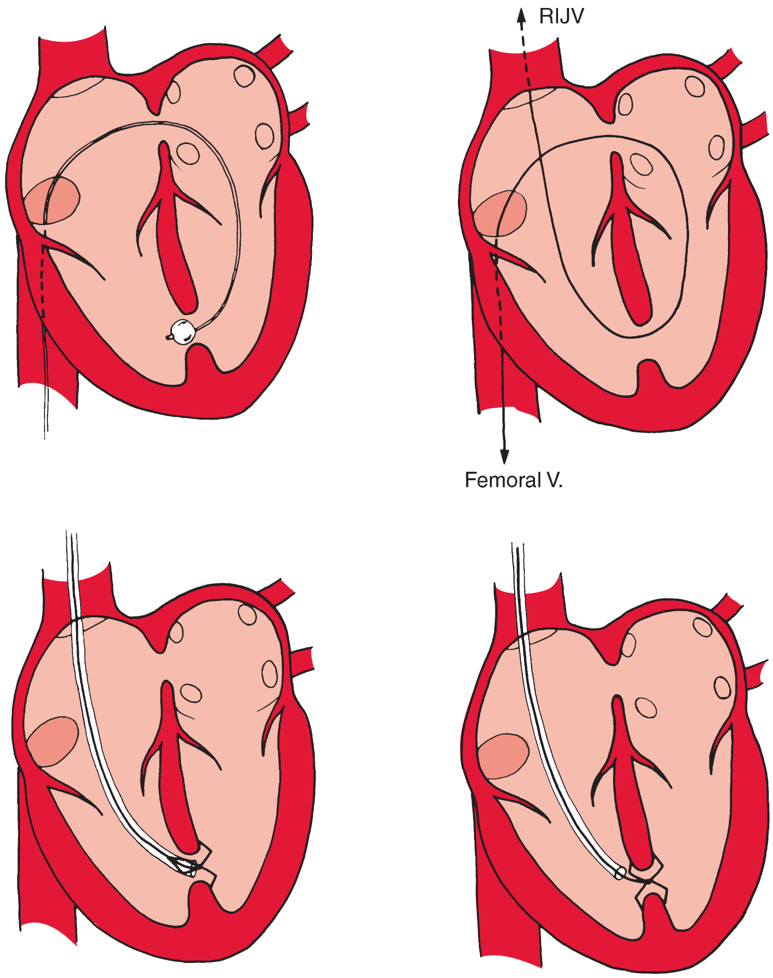


Figure 42–14 Transcatheter technique of ventricular septal defect (VSD) closure. The VSD is more commonly approached from the left ventricular side to ensure guidewire positioning through the greatest portion of the hole. After "snaring" the guidewire, the device is typically deployed from the systemic venous circulation. RIJV, right internal jugular vein. (See text for discussion).

anatomically distant from the aortic valve (not the commonly encountered congenital perimembranous VSD), or with post–myocardial infarction (MI) ventricular septal rupture.

Transcatheter closure technique requires significant operator experience to reduce procedural morbidity and is one of the most technically demanding of interventional catheter procedures performed in our laboratory (Fig. 42–14). A guidewire is typically placed from a transseptal approach (occasionally a retrograde arterial approach is used, especially in patients with TOF with postoperative residual patch-margin defects) into the left atrium and ventricle and across the VSD. The left-to-RV approach assists subsequent passage of a balloon flotation catheter through the widest portion of the defect. The guidewire is snared and delivered from either the contralateral femoral vein or a jugular vein, depending on the location of the defect. Balloon stretch sizing of the central portion of the defect may assist choosing device size. A curved guiding sheath follows the guidewire through the right or left side of the heart across the central channel of the defect. A device system is delivered in a fashion similar to the technique described for ASD closure. The guiding sheath frequently traverses the intraventricular septum at an acute angle, making fluoroscopic confirmation of arm positioning difficult during deployment. The use of transesophageal echocardiography greatly assists in appropriate placement of the arms of the device and successful closure of the defect.

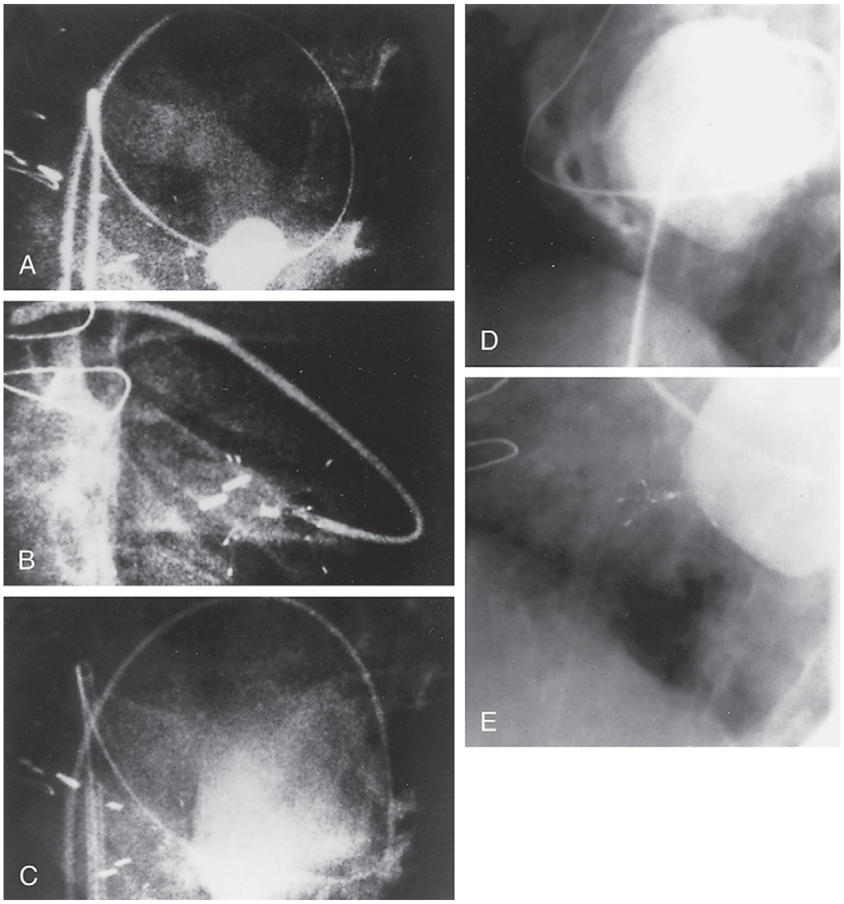


Figure 42–15 Balloon stretch sizing (**A**) of the central necrotic portion of a postoperative residual patch margin defect after primary surgical repair of ventricular septal rupture (VSR) following myocardial infarction (MI) in a patient requiring mechanical inotropic support. Transseptal deployment of a Clamshell occluder (**B**) leads to modest acute decrease in angiographic shunt (**C**), but patient markedly improves to NYHA II symptoms. Shunt flow (**D**) can be totally eliminated (**E**) in some patients with postoperative residual shunting after VSR following MI. Angiograms are performed in left anterior oblique position, with caudal angulation. Sternal wires are thrown to the left portion of the angiograms. Patient's head is towards the top of the page. In **(A),** a guidewire arteriovenous loop has been placed from IVC (*bottom left*) vertically throught the RA, (in circular fashion) transseptally to the LA (*top middle*), to the LV (vertically towards the right) across the VSR (sizing balloon is inflated within the defect) to the RV and back to the RA (wire overlap towards the mid left portion of the angiogram) and back through the IVC and exteriorized out the femoral venous vessels. In **(B),** a clamshell occluder has already been deployed within the defect, and radio-opaque markers are visualized on the distal tips of the 4 RV and 4 LV (2 superior and 2 inferior on each side) device arms. The device remains attached to its delivery system. Contrast injection **(C)** is performed within the LV **(C)** while the device is still attached to its delivery system, demonstrating persisting transseptal shunt (contrast seen towards the bottom left of the angiogram, within the RV). Radio-opaque device markers are not well visualized. After device release (**D** and **E**), the device shifts in position, more firmly sealing the defect, and preventing residual shunting in this patient. Contrast injections within the LV (rightward within the angiogram) fail to demonstrate shunt to the RV. The radio-opaque device markers are better seen **(E)**, especially on the leftward RV side of the septum.

Review of procedural, short-term, and intermediate-term outcomes of transcatheter muscular VSD closure has been most rigorously reported using double-umbrella devices in 170 highly complex and highest-risk patients, with predefined assessment of adversity and outcomes scales.[151] Procedural success was high, with successful implant in 99% of patients, with accompanying marked improvement in clinical severity scale. Potential for device-related adversity was considerable (seen in 20% of patients), and similar patients and families should be appropriately counseled.

Post–Myocardial Infarction Ventricular Septal Rupture

Although surgical advances have dramatically improved the short- and intermediate-term survival of adults with ventricular septal rupture (VSR) after MI, operative risk remains substantial and may be compounded by the location of the VSR, the presence of right or left ventricular dysfunction, multiple organ system failure, medical comorbidities, or prior incomplete surgical attempt at repair. Since February 1990, we have used double-umbrella closure devices (most recently cardioSEAL and cardioSEAL-Star-Flex devices, with only the cardioSEAL approved for limited indications) in attempts to limit VSR after MI. Primary "acute" ventricular septal rupture typically forms a serpiginous tract with a wide (18 to 21 mm) necrotic "lake" within the septum. More mature defects and postoperative patch margin dehiscence defects ranged from 8 to 25 mm by maximal balloon stretching (Fig. 42–15). To date, we have not encountered a defect that was not anatomically or procedurally amenable to device implantation, although success widely varies with techniques and devices used. To date, single-center experience of transcatheter closure of post-MI ventricular septal rupture closure remains anecdotal, though encouraging. We expect future trials of a more aggressive combined transcatheter-surgical strategy with larger devices and an intense medical-surgical collaboration in an attempt to offer prolonged improvement in those patients felt to be at extreme surgical risk.

Perimembranous Ventricular Septal Defect Closure

The use of specifically designed, investigational AGA Amplatzer membranous devices in the closure of perimembranous VSDs has been reported in single-center and multicenter studies. Experience is limited, indications for use are unclear, adversity remains not fully defined, and further study is required.[153,154]

Recommendations

Transcatheter device closure (particularly using double-umbrella CardioSEAL devices) of native or postoperative residual VSDs anatomically distant from the aortic valve has reduced the need for operation, as well as operative morbidity, in many patients with complex defects. At present, until larger devices are available, closure of a ventricular septal rupture after MI appears most successful when orchestrated by a combined surgical-medical team employing a strategy of expeditious primary surgical repair followed by transcatheter device closure of a residual defect, as required. Because of the technical demands of these procedures, transcatheter device closure of VSD and post-MI ventricular septal rupture remains limited to few centers.

Postoperative Residual Defects, Collaterals, and Fenestrations

Embolization coils and occlusion devices have been used in adults (as in children) at high or prohibitive surgical risk to successfully eliminate the following:

- Residual central aorta or systemic artery to pulmonary artery shunts or collaterals
- Systemic venous-to-pulmonary artery or pulmonary venous shunts or collaterals
- Interatrial baffle communications or iatrogenic Fontan fenestrations
- Left superior or inferior vena caval connections to the left atrium
- Coronary artery fistulae
- Systemic and pulmonary arteriovenous malformations
- Paravalvar leaks (Fig. 42–16)

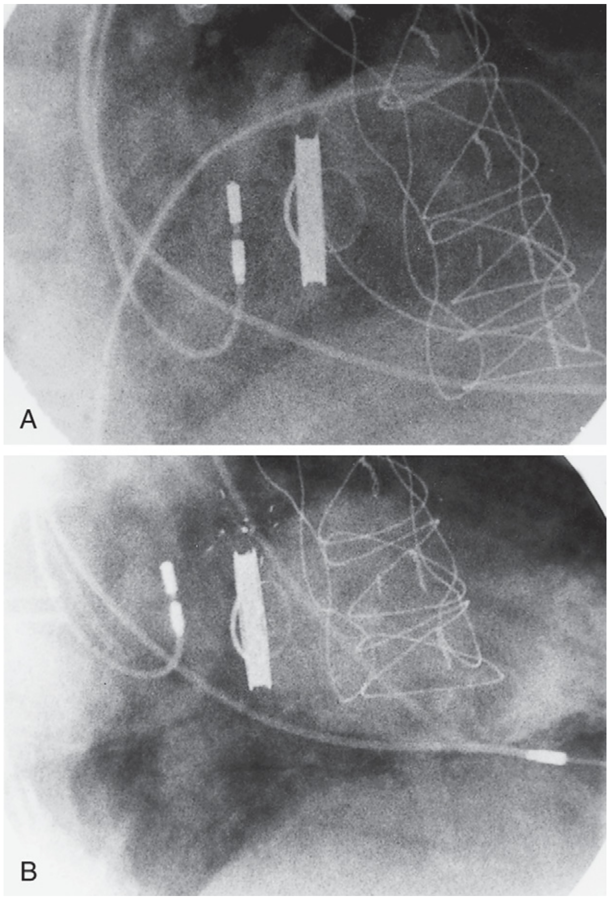


Figure 42–16 Paravalvar mitral regurgitation (**A**) resulting in left atrial hypertension and dyspnea is eliminated after placement of an occlusion device (**B**), with resolution of symptomatology. In **(A),** angiography (over a guidewire placed transseptally from the IVC—off the bottom of the angiogram—vertically through the RA to the LA and via the paravalvar leak—horizontally and superiorly in the angiogram—to the LV) demonstrates superior paravalvar passage. Patient had left atrial hypertension and dyspnea, which were eliminated after closure of the tract passage with a CardioSEAL occlusion device **(B)**. The radio-opaque distal markers of the device are seen superior to the prosthesis ring.

The investigational nature of most of the transcatheter techniques discussed in this chapter, as well as the need for their continued use and for further exploration of novel therapeutics, has been underscored in ACC/AHA guidelines on interventional catheterization in patients with congenital heart disease.[155] This is in large part due to the growing complexity seen in the adult "survivor" with congenital heart disease, coupled with past difficulties in conducting large-scale randomized trials. It is our expectation that in addition to improvements in the tools listed here, the near future will see the following, all from transcatheter access, with increasing collaboration between pediatric and adult medical cardiac interventional units and cardiac surgical teams:

- Capacity to locally deliver medical and genetic therapeutic agents
- Ability to implant intravascular and intracardiac valves and semipermanent measuring devices
- Creation of shunts
- Ability to suture, finely excise, and extract

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Treatment of Severe Idiopathic Pulmonary Hypertension

Michael J. Landzberg

CHAPTER CONTENTS

CURRENT STATE OF DIAGNOSIS

Medical and legal discussions surrounding modern use of anorexigens,[1] coupled with increasing understanding of pathophysiology and availability of pharmacotherapies directed at vascular inflammation,[2] have all helped to raise awareness of severe pulmonary hypertension (PHT) for caregivers and patients. Whereas the classification of "primary" (or unknown etiology) pulmonary hypertension (PPH), which was used in earlier editions of this text, comprised a relatively small percentage of pulmonary hypertensive disorders, a newer classification of "pulmonary arteriolar hypertension" (PAH), either of a familial (occurring in ≈ 6% of PAH cases) or sporadic, nonfamilial "idiopathic" (iPAH) nature, has expanded the clinical entity to include various disorders sharing common pathophysiologic and anatomic features of vascular inflammation. Similarities among these syndromes have been sufficient to allow standardized study populations for testing of mechanisms of disease and application of therapeutics.

EPIDEMIOLOGIC ASSOCIATIONS

Multicenter registries established from 1981 through the present[3,4] have determined the prevalence and incidence of iPAH to be 1 to 2/million and 1 to 2/million/year, respectively, and have established a number of exposures or concomitant conditions associated with PAH (Table 43–1). Among the more important of these are scleroderma, especially of the limited skin involvement type, with estimated prevalence of PHT of 12% to 14%; HIV, with estimated cumulative incidence of 0.5%; and portal hypertension, with estimated prevalence between 0.25% and 2%.[5-7] An association (typically > 2:1) with female gender remains unexplained and persists for PAH associated with many other triggers. The tremendous differences in therapy and outcomes for patients with severe PAH associated with valvular or myopathic heart disease, or proximal or distal chronic thromboembolic disease, mandate a thorough search for "secondary" etiologies (Table 43–2).

Analyses of epidemiologic databases have suggested similar, untreated survival of patients with severe PAH regardless of etiology, with median survival between 2.8 and 3.4 years for the affected adult patient (Fig. 43–1). Survival correlates with variables relating to right ventricular function (typically assessed by hemodynamic measure of systemic cardiac output/mixed venous oxygen saturation and right atrial pressure) and physical capacity (typically measured by 6-minute walking capacity).[8] The improved survival seen in persons with severe PAH associated with Eisenmenger syndrome, or shunt-related PHT with associated cyanosis (10- to 20-year survival > 80%),[9] suggests that increased pulmonary afterload is better tolerated when it is shared between right and left heart chambers.

CURRENT PATHOBIOLOGIC PARADIGM OF IPAH

An important concept in the pathophysiology of iPAH is that exposure to specific triggers in an individual with an underlying genetic predisposition initiates a cascade of events that lead to the development of iPAH. Although various potential triggers have been identified, our understanding of the vascular biology of this disease continues to hold that abnormalities of the pulmonary vascular endothelium are central to the pathophysiologic process. Endothelial injury may initiate a cascade including endothelial dysfunction, growth factor and cytokine imbalance, coagulation abnormalities, and platelet-endothelial cell-leukocyte imbalance. Imbalance of "vasomodulators" including mitogens; vasoconstrictors; and vasodilators, such as endothelin, prostacyclin, nitric oxide, and their controlling substances, contributes to inflammation (Fig. 43–2). These in turn lead to pulmonary vasoconstriction, vascular smooth muscle (SM) cell proliferation, thrombosis in situ, and further vascular injury.

DIAGNOSIS AND RISK STRATIFICATION

Persons with PHT typically come to attention either due to symptoms (dyspnea, chest fullness or pain, bloating, volume retention, palpitations, or syncope), incidentally during evaluation for other disease, or during screening for PAH among

families or patients with identified risks. Typically, diagnosis may be suggested by evidence on cardiac examination of right ventricular failure or a loud pulmonary component of the second heart sound but is strengthened by echocardiography, with estimates of right ventricular and PA pressures ascertained by measure of Doppler-based tricuspid velocities. In general, systolic PA pressures > 50 mm (or ½ systemic levels) or < 36 mm (or ⅓ systemic levels) tend to define or exclude diagnosis of PHT, with intermediate values frequently requiring further assessment. Although echocardiography does reliably assess systolic ventricular function, it can only estimate pressures and diastolic cardiac function. Thus, confirmatory testing relies on hemodynamic assessment at cardiopulmonary catheterization. Typically, this includes measurement of right- and left-sided pressures, flow, and resistance (assisting in diagnosis and prognostic assessment); limited angiography as indicated; and maneuvers to test reactivity of pulmonary flow and resistance to acute administration of pulmonary vasodilator agents (typically inhalation of nitric oxide with or without oxygen, inhalation, or intravenous administration of specific prostanoids or acetylcholine or adenosine). Catheterization should be performed in regional specialty centers to decrease associated risk and improve reliability of diagnosis and testing. In general, catheter-based measurement of mean PA pressure > 25 mm (or systolic pressure > ⅓ to ½ systemic levels) defines PHT. Exercise-induced PHT remains less well defined but is suggested when mean PA pressure rises to > 30 mm Hg on exertion.

Response to acute administration of pulmonary vasodilator therapy has classically been described as a ≥ 20% decrease in systolic PA pressure with stability or improvement in pulmonary blood flow; this response is observed in 10% to 20% of tested patients, potentially reflecting a subset of patients with an earlier, or less lethal, phase of disease. Although a positive vasodilator response was initially felt to correlate with improved functional and survival outcomes in response to therapy with calcium channel blocker (CCB) therapy (>80% five-year survival),[10] a contemporary study has suggested a lesser correlation of percentage reduction in PA pressure with long-term responsiveness to CCB therapy and has led to a suggestion of adding an absolute fall of mean PA pressure to ≤ 35 mm Hg to be classified as a "responder." This more stringent definition of response improves prediction of improvement with CCB therapy.[11] In the past, acute vasodilator responsiveness was critical to risk stratification and choice of therapy and still carries importance for both aspects of care. However, favorable long-term effects on PA pressure, functional capacity, and survival have been documented with newer agents (prostanoids, endothelin antagonists) among patients who do not demonstrate acute vasodilator responsiveness, raising new hope for such patients.

Accurate differential diagnosis and elimination of additional treatable etiologies for PAH mandate additional patient testing, typically including CXR; pulmonary function testing including measurement of diffusion capacity; high-resolution chest CT scan, typically with angiography and pulmonary embolism protocol; serological testing (collagen vascular screening, liver and renal function, complete blood count and assessment, HIV testing when appropriate); abdominal ultrasound with or without flow assessment in the portal veins or liver-spleen scintigraphy when appropriate; sleep testing as appropriate; and TB testing when indicated (see Table 43–2). Disease-specific therapies including oxygen administration, positive airway ventilation, alternative organ therapy or transplantation, surgical pulmonary endarterectomy,[12] or balloon

Table 43–1 Exposures and Conditions Associated with Pulmonary Arteriolar Hypertension

Anorexigens (Dexedrine, aminorex, fenfluramine)
Catecholamines (cocaine, pheochromocytoma)
Portal hypertension/cirrhosis
Connective tissue diseases (scleroderma, mixed connective tissue disease, systemic lupus, rheumatoid arthritis)
Infection (HIV, tuberculosis, schistosomiasis)
Chronic lung disease, hypoxia, sleep apnea
Large-volume or high-pressure intracardiac or intravascular shunting
Myeloproliferative disorders
Sickle cell disease/hemoglobinopathies/platelet diseases
Toxin ingestion (L-tryptophan, toxic oil)

Table 43–2 Causes of Secondary Pulmonary Hypertension and Potential Studies to Elucidate the Diagnosis

Secondary Causes of PHT	Possible Diagnostic Studies
Chronic thromboembolic PHT	V/Q scan, CT or direct angiography
Pulmonary vein obstruction	MRI, CT, catheterization
Congenital heart disease	Echocardiography, MRI
Left atrial hypertension	Echocardiography, BNP, hemodynamic measure
Pulmonary airway disease	PFT, ABG
Hypoventilation	Sleep apnea testing
Interstitial lung disease	PFT, ABG, chest CT
Rheumatologic disease	Serology, tissue biopsy, chest CT
Cirrhosis	LFTs, ultrasound, CT, biopsy
Peripheral pulmonary stenosis	V/Q scan, angiography, MRI
Hemoglobinopathies	CBC and smear, electrophoresis

ABG, arterial blood gas; BNP, B-natriuretic peptide; CBC, complete blood count; CT, computed tomography; LFT, liver function test; MRI; magnetic resonance imaging; PFT, pulmonary function testing; PHT, pulmonary hypertension; V/Q, ventilation-perfusion.

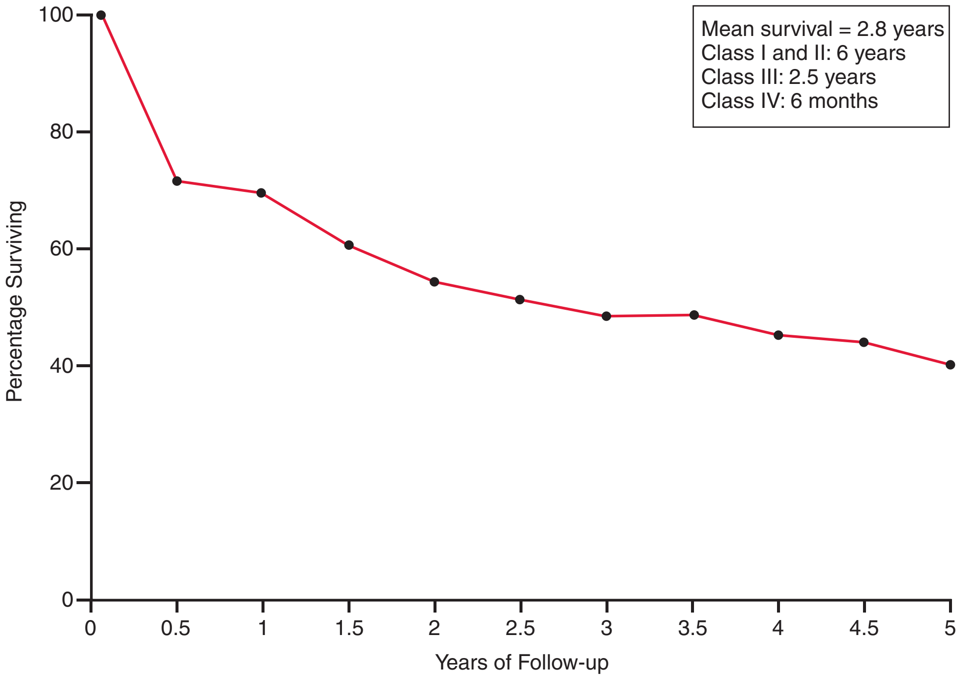

Figure 43–1 Untreated survival with severe PAH. (Modified from D'Alonzo GE, Barst RJ, Ayres SM: Survival in patients with PPH: Results from a National Prospective Registry. Ann Intern Med 1991;115:343-9.)

pulmonary angioplasty[13,14] may be indicated as primary therapy on the basis of the results of such testing.

Functional capacity, as assessed by exercise testing, with formal measurement of 6-minute walking capacity (typically used due to ease and patient functional restriction) or cardiopulmonary exercise testing with measurement of maximal oxygen consumption,[15] has become routine as a prognostic tool, both for initial survival prediction and response to therapy. Subjective assessment of functional capacity using NYHA or WHO functional scales has correlated with both untreated and treated outcomes and has been used to define populations in randomized controlled trials.[16] Dyspnea scales have been used in randomized controlled trials, although their individual additive prognostic potential remains undefined. Serologic testing of biomarkers including troponins and measurement of natriuretic peptides remains under investigation but appears promising as markers of disease severity.

CURRENT STATE OF THERAPY

CCBs were the first widely accepted therapeutic agents for patients with PAH. Their use was modeled on the "vasoconstrictor" model of pulmonary arteriolar hypertension, envisioning pathology to be due to a disorder and disregulation of small pulmonary arteries, characterized by lamellar intimal fibrosis, medial hypertrophy, and neovascular plexiform lesions. To date, no randomized trial exists that tests effect and risk of CCB, although nifedipine has remained the prototype therapy for the small percentage of patients (5% to 15%) who are "responders" to acute administration of vasodilator agents during cardiopulmonary catheterization. Given that clinical effect typically requires drug doses 5- to 10-fold higher than those commonly used to treat hypertension and that such dosage requirements are unpredictable and may be accompanied by considerable adverse effects, dose-response testing is typically performed with indwelling PA pressure monitoring to identify eventual effective target dosage. Most centers will recommend achieving this goal dosage in a graded fashion to allow adverse effects to be minimized as the systemic vasculature accommodates to the drug effect. More recent uncontrolled databases suggest that CCB use may be even less effective than previously thought[17] and may require a change to a more stringent definition of "acute vasodilator responsiveness" to better define the population for whom this class of medication will be effective. CCB therapy is generally believed to be contraindicated in those patients presenting with substantial right atrial pressure elevation or marked decrease in cardiac output.

The use of what is considered "conventional" PAH therapy including warfarin, oxygen, digoxin, and diuretics is controversial. Benefit of warfarin has been extrapolated from subset analyses of retrospective single center studies and is based on pathologic data from lung biopsies and postmortem examinations, confirming in situ thrombosis within the pulmonary vasculature. Warfarin is generally advised, with a target INR of 2.0-3.0, dependent on individual patient risk of bleeding. Multicenter randomized controlled trials of other therapeutic agents for PAH have noted use of oral anticoagulants at time of inclusion in 51% to 86% of enrolled patients.

Long-term digoxin administration for patients with right heart dysfunction due to PAH has not been studied. Its use has been declining, with digoxin administration at time of inclusion in multicenter RCTs in 18% to 53% of subjects. Diuretic therapy may assist in volume control and is likewise unstudied in the chronic state, and its use has been documented in 49% to 70% of patients during multicenter RCTs of other therapies for PAH. Use of oxygen, other than that defined for appropriate patients with chronic lung disease and hypoxemia, is unsupported.

Over the past decade, the "vasoconstriction" monolayer model of iPAH has been replaced with the vascular wall inflammation paradigm discussed earlier, with the introduction of novel therapies reflecting this change in pathobiologic

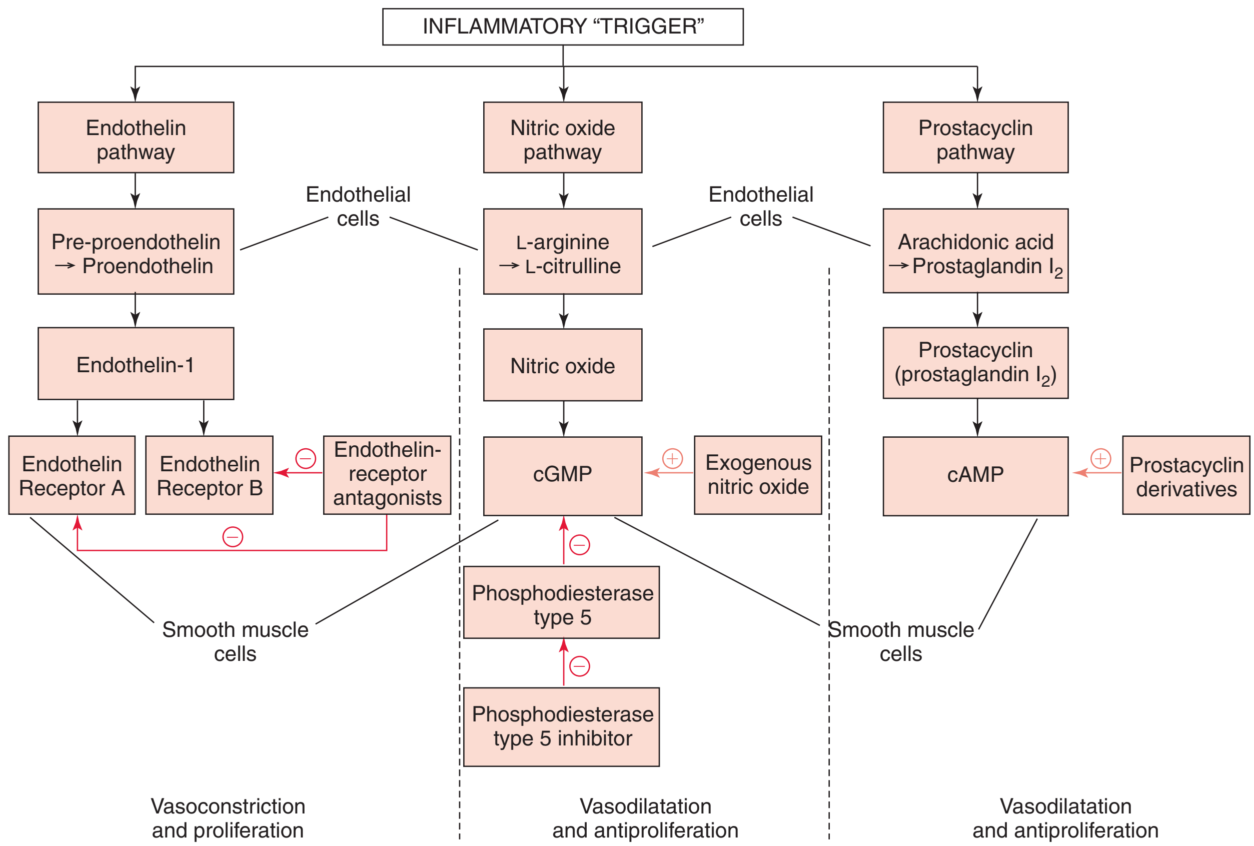

Figure 43–2 Current vascular inflammation and constriction model of iPAH. (Modified from Humbert M, Sitbon O, Simmoneau G: Treatment of pulmonary arterial hypertension. N Engl J Med 2004;351:1425-36).

thought. For the majority of affected patients, modern treatment focuses on mediators of chemotaxis, cellular proliferation and differentiation, and regulation of vasoactive peptides and growth factors. These mediators currently include prostanoids (intravenous, inhaled, oral), endothelin antagonists, nitroso-compounds, and phosphodiesterase inhibitors.

Prostanoids

Earliest multicenter randomized clinical trials focused on the use of the intravenous prostanoid, epoprostenol. Patients treated with epoprostenol + conventional therapy showed improved survival and exercise tolerance, increased cardiac output, and decreased pulmonary vascular resistance when compared with controls using conventional therapy alone.[18] These results have been confirmed both in patients with iPAH, as well as in patients with PAH associated with scleroderma. Longer-term benefit had been demonstrated in multiple subsequent studies (Fig. 43–3).[19] However, the personal and financial costs of epoprostenol use are protean, with a need for continuous administration via a commercially available personal pump attached via tubing to a centrally placed indwelling catheter and daily personal admixture of drug. Common drug side effects include flushing, headache, peculiar jaw pain with the first bite of each meal, boney and muscular pain, local and systemic infection, nausea, diarrhea, hypotension, tachyphylaxis, and potential for severe and potentially life-threatening rebound PHT on drug withdrawal. Typical dosing begins at 0.5 to 2.0 ng/kg/minute, with adjustments based on effect and tachyphylaxis, typically every 3 to 10 days. Eventual "plateauing" of dose may occur, without the need for dosage augmentation. Periodic invasive hemodynamic assessment is required to ensure adequacy of dosage, as well as avoidance of overdosage. This medication is currently FDA approved for PAH patients who are in functional class III-IV. Pharmaceutical cost may range from \$75,000 to \$150,000 yearly. Drug benefit is modest including improved 6-minute walk distance of 20 to 30 m and extension of survival to 63% at 3 years. Predictors of survival at the start of therapy have included functional class (poor prognosis if initial 6-minute walk < 250 m), cardiac index, mean right atrial pressure (poor prognosis if ≥ 12 mm Hg), and mean PA pressure, with predictors of survival after 1 year of therapy including improvement in cardiac index and decrease in right atrial pressure. The strongest predictor of long-term survival may be the ability to achieve a 6-minute walk ≥ 380 m.[19a]

Multicenter randomized clinical trials, all of which have required right heart catheterization for entry, have shown favorable effects for other prostanoids and include the following:

- The Treprostinil (SQ prostanoid; tricyclic benzidine analogue of prostacyclin) Study[20]: This was a 12-week, double-blind, randomized, controlled trial including 470 patients (81% women), 271 with iPAH, 90 with connective tissue disease, 109 with congenital heart disease, with a mean age of 44 years at enrollment. Functional capacity was WHO Functional Class (FC) II (12%), III (81%), IV (7%), with a

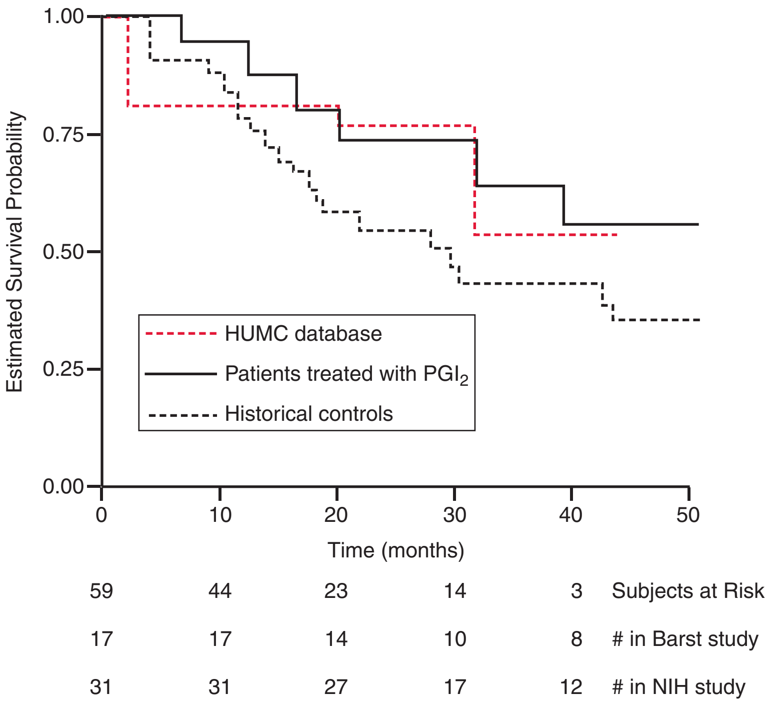

Figure 43–3 Survival in severe PAH: treatment with epoprostenol. (Modified from Shapiro SM, Oudiz RJ, Cao T, et al: Primary pulmonary hypertension: Improved long-term effects and survival with continuous intravenous epoprostenol infusion. J Am Coll Cardiol 1997;30:343-9.)

mean baseline 6-minute walk distance of 327 m. Study drug was started at 2 ng/kg/minute, with weekly dosage increases and endpoints measured at 12 weeks including 6-minute walk and hemodynamic parameters. At trial conclusion, there was only a 10-m difference in 6-minute walk distance between the study groups. However, this difference increased as the final tolerated drug dosage increased, with 36.1 ± 10 m difference between groups when the study drug dosage was > 13.8 ng/kg/minute. Benefits persisted at 18 months of therapy, with the most common side effect being infusion-site pain. This medication is currently FDA approved for patients with PAH and WHO FC III or IV and has the benefits of being a more stable compound, requiring a smaller mechanical pump, and a nonintravenous administration. Local injection-site pain has been frequent, though various strategies have been designed to reduce such. Financial cost per year has been estimated (Medical Letter-2002) at $93,000.

- The Beraprost (oral prostacyclin analog) ALPHABET Trial[21] Study: This was a 12-week double-blind randomized controlled trial that enrolled 130 patients, 62% of whom were women, 63 with PPH, 13 with connective tissue disease, 24 with congenital heart disease, 21 with portal hypertension, 9 with HIV, and with mean age at enrollment of 45 years. Functional capacity at enrollment was WHO FC II (50%), III (50%), and IV (0%) with a mean baseline 6-minute walk of 373 m. The study drug was started at 20-mcg po qid, with weekly dosage increases, with a maximal dose of 120 mcg qid (mean 80 mcg qid), with endpoints measured at 12 weeks including 6-minute walk and hemodynamic parameters and Borg dyspnea index. At trial end, there was nearly a 30-meter difference in 6-minute walk distance between the study groups. This difference was more pronounced in patients with iPAH compared with those with other recognized triggers of PAH. Continued drug benefit after 1 year of therapy was lost in a subsequent trial, and this agent is currently not FDA approved for use in PAH.[22]
- The Iloprost (inhaled prostacyclin analog) AIR Trial[23] Study: This was a 12-week, double-blind randomized trial, with enrollment based on baseline 6-minute walk (mean 323 m). Study drug was started at 2.5 to 5.0 mcg inhaled 6 to 9 x/daily with overnight "breaks," with dosage adjustments over the first 8 days and assessment at 12 weeks of a combined endpoint defined as 10% improvement of 6-minute walk plus improved WHO FC, hemodynamic parameters, Borg dyspnea scale, and quality of life scale. Of the 203 patients enrolled, 67% were women—102 with iPAH, 35 with connective tissue disease, 57 with chronic thromboembolic PAH, 9 anorexigen-related PAH, with mean age at enrollment of 51 years and functional capacity at enrollment of WHO FC II (0%), III (59%), and IV (41%). At trial end, 17% of iloprost-treated patients compared with 4% of placebo-treated patients achieved a primary endpoint; there was a 36-meter difference in 6-minute walk distance between the study groups (Fig. 43–4). This difference was more pronounced in patients with iPAH compared with those with other recognized triggers of PAH. Iloprost is currently FDA approved for patients with PAH and WHO FC III or IV, with estimated cost of treatment $60-70,000/year.

Endothelin Receptor Antagonism

The BREATHE series of trials have assessed the safety and efficacy of a combined endothelin α- and β-receptor antagonist, bosentan, in the treatment of iPAH and other forms of PAH.

The BREATHE-1 (bosentan: combined endothelin α- and β-receptor antagonist) Study[24] was a 16-week, double-

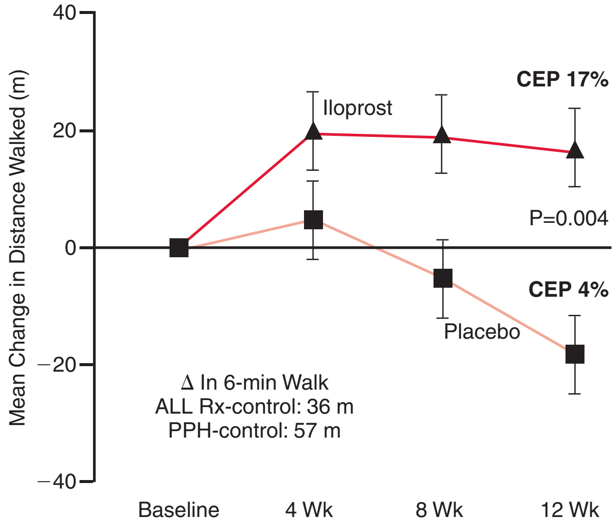

Figure 43–4 Functional capacity in severe PAH: treatment with iloprost. (Modified from Olschewski H, Simonneau G, Galie N, et al: Inhaled iloprost in severe pulmonary hypertension. N Engl J Med 2002;347:322-9.)

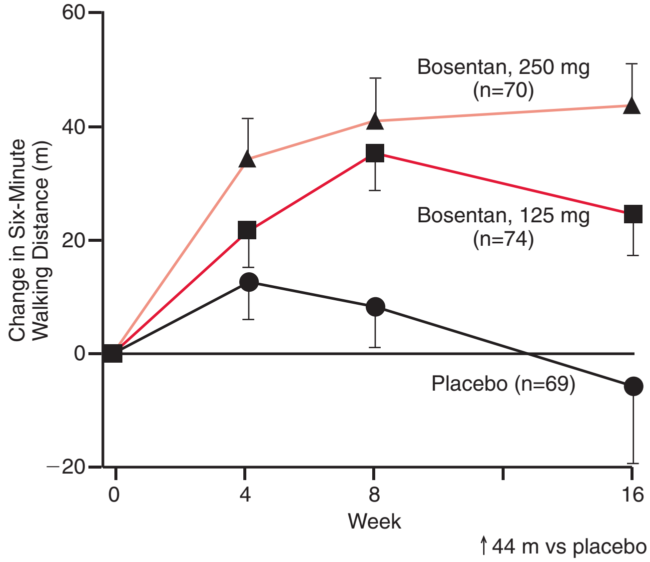

Figure 43–5 Functional capacity in severe PAH: treatment with bosentan. (Modified from Rubin LJ, Badesch DB, Barst RJ, et al: Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-303.)

blind, randomized trial with enrollment based on a baseline 6-minute walk (mean 335 m). The study drug was started at 62.5 mg bid × 4 weeks with 2 arms of dosage increase to either 125 or 250 mg po bid × 12 weeks. Endpoints were measured at 16 weeks including 6-minute walk and hemodynamic parameters, Borg dyspnea scale, and WHO FC. Of the 213 patients enrolled, 79% were women—151 with iPAH, 62 with connective tissue disease, with mean age at enrollment of 48 years, with functional capacity at enrollment of WHO FC II (0%), III (92%), and IV (8%). At trial end, a 44-m difference in 6-minute walk distance existed between the study groups (Fig. 43–5). Benefits have persisted during long-term follow-up, with the most common side effects being LFT abnormalities (mandating monthly LFT checks) and mild dilutional anemia. The FDA has approved bosentan use in patients with PAH in FC III or IV. The cost per year is $36,000 (Medical Letter—2002).

Phosphodiesterase Inhibition

Phosphodiesterase (PDE) inhibition (in particular, of PDE-5) blocks metabolism of cyclic GMP, enhances cGMP-mediated relaxation and growth inhibition of vascular smooth-muscle cells in the lungs of patient with iPAH, and potentially improves clinical outcomes. Several trials have led to FDA approval of this therapy for patients with iPAH.

The Sildenafil Citrate (phosphodiesterase type 5 inhibitor) Study[25] was a 12-week, double-blind, randomized trial, with enrollment based on baseline 6-minute walk (mean 344 m). The study drug was prescribed at either 20-mg, 40-mg, or 80-mg dosages, each administered three times daily, with endpoints measured at 12 weeks including 6-minute walk and hemodynamic parameters, Borg dyspnea scale, and WHO FC. Of the 277 patients treated, 75% were women—175 with iPAH, 87 with connective tissue disease, and 18 with repaired congenital systemic-pulmonary shunts. The mean age at enrollment was 49 years, with functional capacity at enrollment of WHO FC II (39%), III (58%), and IV (3%). At trial end, there was a 45- to 50-m difference in 6-minute walk distance between the sildenafil-treated groups and placebo, with no statistically significant differences among the different dosage sildenafil-treated arms. Benefits persisted during 1-year follow-up, with most common side effects being flushing, dyspepsia, and diarrhea. The FDA has approved sildenafil use in patients with iPAH. The cost per year is currently approximately $13,000.

Similar trials using sole endothelin A antagonists and combined therapies are under way and remain to be completed or interpreted.

Atrial Septostomy

The rationale for an atrial septostomy as therapy for patients with iPAH is based on the suggestion that the presence of an atrial septal defect or patent foramen ovale appears to confer a benefit in patients with iPAH.[26] It has been suggested that an intra-atrial defect with right-to-left shunting preserves forward cardiac output, at the expense of arterial desaturation, in the setting of severe PHT, right ventricular dysfunction, and low cardiac output. One cohort study reported survival benefit compared with historical control subjects.[27] However, procedure-related morbidity and mortality are high, and randomized studies have not been reported, making such therapy a reasonable option only in centers with considerable expertise, and where alternative therapy as a bridge to transplantation is unavailable.

Transplantation for iPAH

Single-lung, double-lung, and heart-lung transplantation have been used for patients with severe iPAH, with 5-year survival postprocedure still hovering at approximately 50%.

Procedural morbidity and mortality are much higher for transplantation for iPAH, as compared with other forms of lung disease. Until quality of life indices or survival benefit is improved with changes in surgical techniques and medical support, transplantation should be reserved for patients with iPAH refractory to medical therapy. However, in view of variability in individual patient prognosis, and in anticipated waiting times before transplantation, the timing for referral may vary by institution.

MEDICAL THERAPY ALGORITHMS

Prescription of current intravenous and nonparenteral therapies for PAH in the United States focuses on FDA-approved therapies, administered to patients in a particular WHO functional classes in which the approved medications were tested (e.g., epoprostenol or iloprost for FC IV patients; bosentan, treprostinil, iloprost, or sildenafil for patients in FC III). If patients do not respond to initial diagnostic acute vasodilator challenge, we recommend the following therapy (Fig. 43–6):

WHO FC II: United States: sildenafil, bosentan (tested in FC III patients), or treprostinil elsewhere: also short-term Beraprost or long-term iloprost

WHO FC III: United States: bosentan, sildenafil, iloprost, or treprostinil elsewhere: also short-term Beraprost

WHO FC IV: United States: epoprostenol, iloprost (consideration of bosentan or sildenafil, if 4 to 12 weeks from drug start until substantive clinical drug effect is achieved, is believed to be safe)

Patients without improvement to < FC III or 6-minute walk distance ≥ 380 m by several months of therapy, those initiating in FC IV, or those persisting with elevated RA pressure or low systemic cardiac output are typically referred for consideration of multi-drug therapy or organ transplantation (single lung/double lung/heart-lung depending on institutional availability and success).[19a,28] Worsening of FC, new symptoms of neurohormonal activation, or decrement in 6-minute walk time > 10% baseline with worsening dyspnea typically prompt a full reassessment for potential causes of deterioration or to alter therapy.

Therapy designed to support right ventricular contractile function, decrease muscular remodeling, decrease neurohormonal activation, decrease inflammation, or even reduce alveolar hypoxia (e.g., with β-blockade, nesiritide, angiotensin-converting enzyme inhibitors or angiotensin receptor blockade, spironolactone), as shown to be of assistance in left ventricular failure syndromes with increased afterload, have not been adequately studied in patients with PAH. Controlled exercise and respiratory training have been shown to improve both exercise capacity and quality of life for patients with severe chronic pulmonary hypertension.[28a] Effects of exercise training, stress reduction, nutritional support, and therapy of sleep abnormalities have yet to be scientifically examined. How to, and when it is best to, combine or transition therapies, as well as elucidation of markers of responsiveness to such therapies, are topics of current investigation. Use of implanted continuous hemodynamic recording devices of RA, RV, or PA pressures have been described, and although their use remains intriguing, proof of clinical benefit has not been demonstrated.

General patient recommendations to practice are (1) safe airline travel (most commercial airlines pressurize to an equivalent of 1800 to 2400 m, with hypobaric hypoxia typically seen at 1500 to 2000 m) with frequent rests and concomitant oxygen use; (2) budgeting of energy to personal

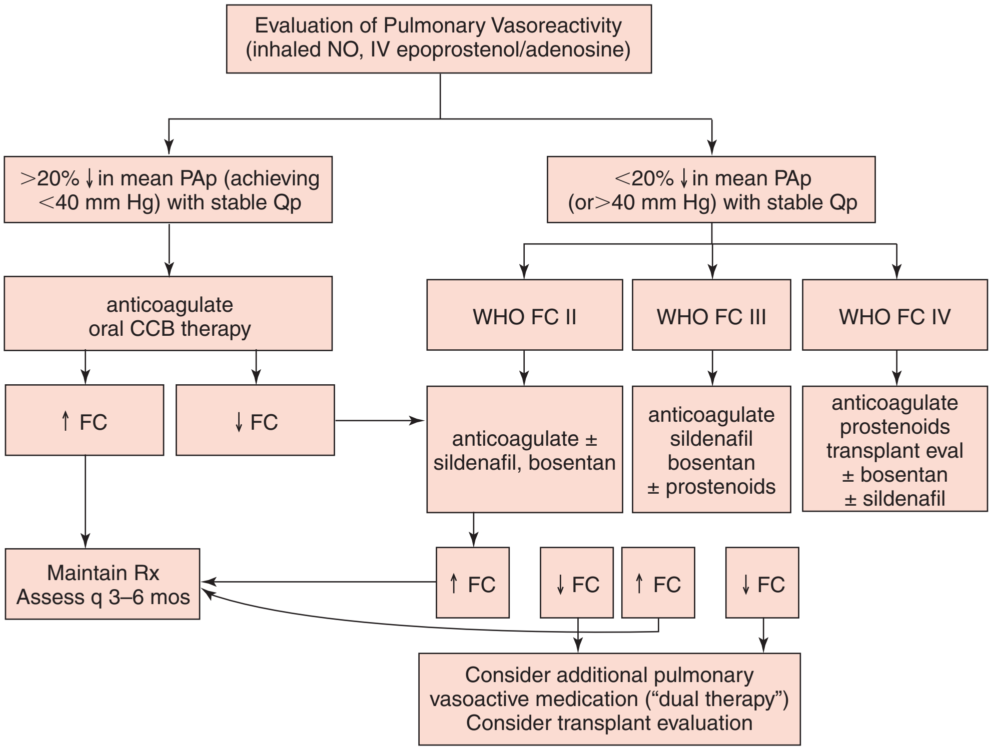

Figure 43–6 Algorithm for the management of iPAH. CCB, calcium channel blocker; ↓ FC: 6-minute walk < 380 m; ↑ FC: 6-minute walk ≥ 380 m; NO, nitric oxide; PAp, mean pulmonary artery pressure; Qp, pulmonary blood flow; Rx, therapy; WHO FC, World Health Organization functional class.

goals; (3) excellent skin, dental, and overall infection control strategies; (4) episodic laboratory checks (autoimmune tests, renal and hepatic function, complete blood count); (5) vigilance regarding the use of even simple, over-the-counter agents with potential for renal- or hepatic-function alterations; and (6) overall educated consumerism.

NEW PATHOBIOLOGIC AND CARE PARADIGMS?

Evidence is increasing for genetically inherited abnormalities in endothelial cell apoptosis and growth potential, with links of familial and sporadic iPAH to a member of the TGF-B superfamily, bone morphogenetic protein receptor BMPR2 (as well as angiopoietin-1, its specific endothelial cell receptor, BMPR1, and ALK 1, encoding a BMPR receptor). Currently, assays for mutations in these genes are not sufficiently standardized to allow for genetic screening, although there is speculation that specific defects may correlate with more robust PAH phenotypes and improved definitions of susceptibility to PAH.[29-31]

Increasing data suggest that the hallmark lesion of iPAH/PAH, the plexiform lesion, is a response phenomenon to local hypoxia or inflammation and represents a tumor-like proliferation of endothelial cells (monoclonal in iPAH, polyclonal in secondary forms of PAH). To date, the functional significance of these lesions and their components and the temporal control of vascular growth remain elusive.[32]

Markers of cellular inflammation, matrix stimulation and cellular growth, as well as platelet and coagulant activity can now be studied in circulation and in situ, with alterations of fractalkine, RANTES, interleukin 1-B, interleukin-6, soluble IVAM, sVCAM, sP-selectin, S-electin, vW factors, serotonin, PAI-1, fibrinopeptide A, and thrombomodulin noted in biopsy samples and circulation of patients with PAH. To date, there remains a need to further characterize, as well as correlate, changes in these factors with disease severity or progression.[33,34]

Endothelial cell (EC) activation abnormalities have been at the heart of modern understanding and therapies for PAH. Successful use of chronic NO has been demonstrated, while randomized clinical trials remain to be orchestrated. Abnormalities in VEGF have been described in patients with PAH, although where these abnormalities lay in the activation of the overall inflammation/constriction scheme and the effect of modulators of these factors remain unknown.

The role of serotonin as a trigger for development of PAH was highlighted by the fen-Phen epidemic, with direct action on PA sM cell 5HT-2A and 5HT-1B receptors.[35] A unified theory of serotonin activation remains to be clearly defined, and trials of serotonin receptor blockers and serotonin transporters have been suggested. Other abnormalities in sM cell components in patients with PAH may include dysfunctional voltage-dependent potassium channels, which can be altered with anorexigenic agents including aminorex, dexfenfluramine, and phentermine.

Increased extracellular matrix production is a hallmark of PAH, with abnormalities of serine elastase, causing elevation in bFGF leading to changes in MMPs, production of tenascin and phosphorylation of growth factor receptors, and sM cell proliferation.[36] Where such abnormalities in matrix activation lay in the overall inflammation/constriction scheme of PAH and the effect of modulators of these factors remain unknown.

PREGNANCY AND CONTRACEPTION

(see Chapter 41)

The risk of pregnancy-related death for women with PAH is substantial, with mortality in the modern era anecdotally similar to that previously reported as 30% to 50%, despite use of modern pulmonary vasoactive agents.[37] For women who present during pregnancy, maternal and fetal risk of termination may be equally substantial, if not greater, depending on timing of presentation. Warfarin-based teratogenic risk may be substantial at doses typically used in PAH therapy. Any such patient maintaining pregnancy is advised to do so only in regional centers of expertise, with access to all levels of supportive maternal and fetal care. Reliable and educated contraception remains a hallmark of appropriate care, whereas appropriateness and effectiveness of individual therapies (in particular, hormonal contraception) remains untested in this population. Tubal ligation, similar to any noncardiopulmonary surgery, may carry substantial morbid and mortal risk in patients with PAH and should not be undertaken without consideration of alternatives.

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Chapter 44

Prevention and Treatment of Endocarditis

Gail E. Peterson and Christopher H. Cabell

CHAPTER CONTENTS

INTRODUCTION

At the time that Sir William Osler eloquently delivered the Gulstonian Lectures in 1885, the understanding of infective endocarditis (IE) was based on clinical observations, autopsy findings, and small case-series. Even today, our knowledge of this disease is primarily based on traditional case-series with relatively small numbers of patients. No randomized trials have been performed to test strategies for prevention, and there are few randomized trials for the treatment of IE. As a result, clinical practice guidelines[1-3] are based largely on expert opinion and practice experience rather than on evidence-based medicine grounded in large-scale trials. The study of IE is hampered further because it is a relatively rare disease, involves diverse underlying risk factors, affects heterogeneous patient populations, and involves a wide array of infecting microorganisms.

DIAGNOSIS

Diagnosis of IE has advanced over the past century with the evolution of standardized diagnostic criteria. In 1994 David Durack and colleagues[4] from Duke University described for the first time new diagnostic criteria that incorporated echocardiographic findings and a history of intravenous drug use.

The clinical utility, sensitivity, and specificity of the Duke criteria have been independently validated and found to have superior performance compared with older criteria that do not use echocardiography.[5-7] As the epidemiology of IE has evolved and basic understanding of the disease process has improved, modifications to the Duke criteria have been proposed. The major criteria have been expanded to include nosocomial *Staphylococcus aureus* (*S. aureus*) bacteremia, and serological criteria for *Coxiella burnetii*.[8] Splenomegaly, elevations in C-reactive protein, elevations in erythrocyte sedimentation rate, and the presence of indwelling intravenous catheters have been added to the minor criteria.[9]

THE USE OF ECHOCARDIOGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF ENDOCARDITIS

Echocardiography, which provides excellent visualization of cardiac anatomy, has contributed to earlier diagnosis and detection of complications. The hallmark lesion of IE is a vegetation (Fig. 44–1A) that is evident in 67% to 86% of cases of definite IE.[10-12] Vegetations typically occur on the low-pressure side of a high-velocity turbulent jet and are often accompanied by other hemodynamic or anatomic abnormalities. When infection invades contiguous structures, an abscess may result (see Fig. 44–1C). This most commonly involves the aortic root and the anterior mitral annulus and may extend into the ventricular or atrial septum, right ventricular outflow tract, and anterior mitral valve leaflet. Periannular extension may result in tissue necrosis and ultimately result in communication between areas that are external to cardiac chambers. Periannular invasion that occurs in the setting of a prosthetic valve can lead to valve dehiscence and perivalvular regurgitation (see Fig. 44–1B).

Transthoracic echocardiography (TTE) is easily performed, noninvasive, and does not require conscious sedation, but in 10% to 15% of adults sound transmission is compromised, by interfering tissue or air attenuation, or both, and leads to poor spatial resolution. Transesophageal echocardiography (TEE) is more invasive and labor intensive but has an improved ability to detect smaller vegetations and complications of endocarditis. The sensitivity and specificity for TTE and TEE are shown in Table 44–1.

During the initial evaluation of patients with suspected IE, the appropriate mode of echocardiography to use depends, in part, on the prior probability of disease.[13,14] Clinical findings that suggest IE are listed in Table 44–2. In patients with a very low probability for IE based on clinical data, echocardiographic findings are unlikely to change the management of the patient.[15,16] Clinical criteria that suggest a higher likelihood of IE include vasculitic or embolic phenomena, presence of central venous access, presence of prosthetic valve, recent IV

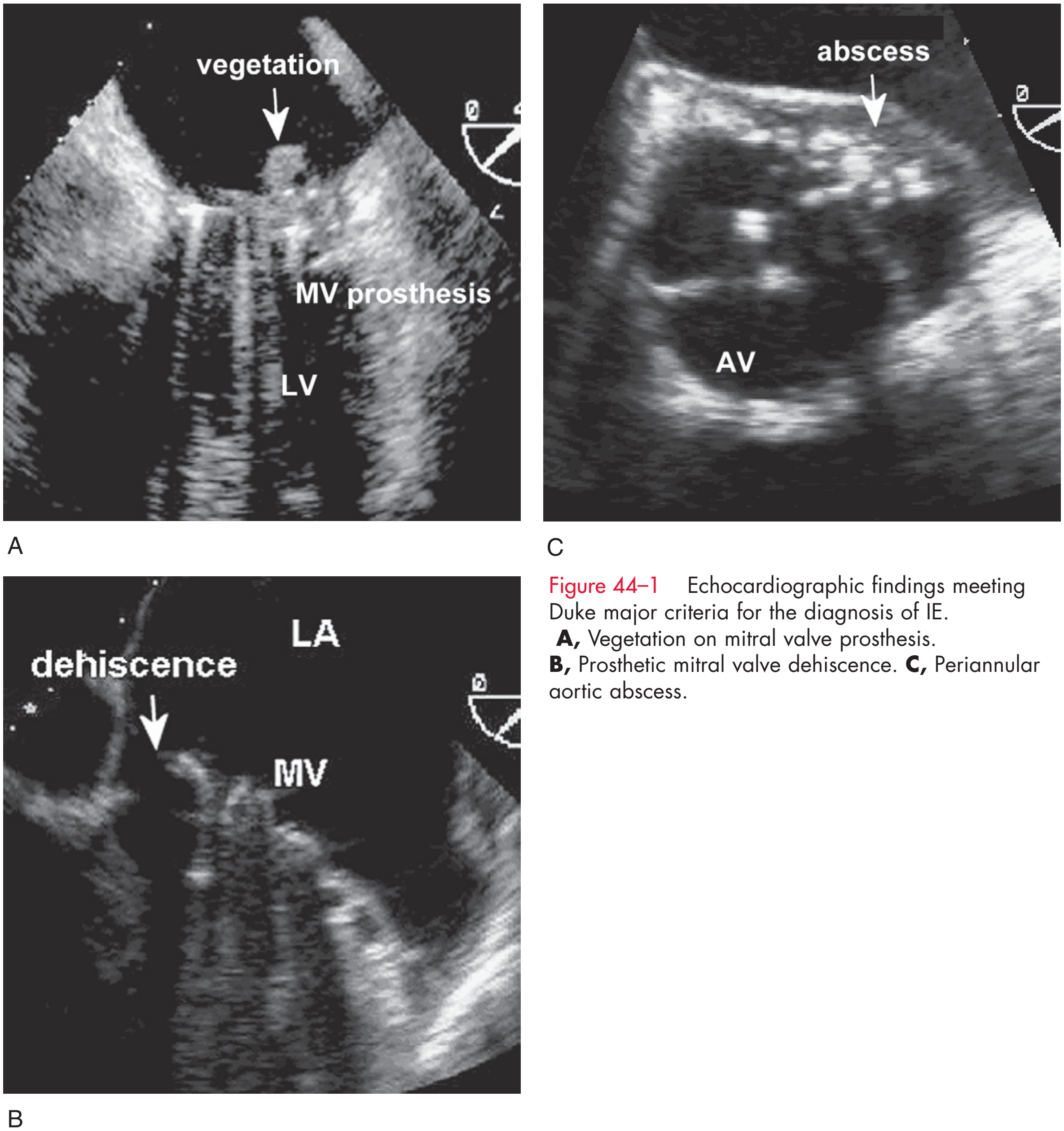

Figure 44–1 Echocardiographic findings meeting Duke major criteria for the diagnosis of IE. **A,** Vegetation on mitral valve prosthesis. **B,** Prosthetic mitral valve dehiscence. **C,** Periannular aortic abscess.

drug use, and positive blood cultures. When these criteria are collectively absent, the likelihood of finding echocardiographic evidence of endocarditis is unlikely.[17] Heidenreich and associates[13] sought to answer the question of which form of echocardiography to select with decision tree analysis and Markov modeling, using published data to simulate costs of care and outcomes of patients suspected of having IE. Based on this analysis, TEE was found to be cost effective for patients with a pretest probability in the intermediate range (i.e., patients with predisposing conditions and bacteremia typical for IE), while TTE was better only for those patients with a very low prior probability of IE. TEE is favored at many institutions for the evaluation of most patients with *S. aureus* bacteremia, and there is supporting evidence that TEE-guided therapy is cost effective for patients with catheter-associated *S. aureus* infections.[14]

Because TEE is more sensitive in detecting complications of IE, such as perivalvular extension and valve perforation, it should be used in patients at risk for these complications. Such patients include those who present with CHF, who develop new heart block, and who have persistent fever or bacteremia during appropriate antimicrobial therapy. TEE should also be used as the initial examination in the setting of the presence of prosthetic valves and intracardiac devices because of the low sensitivity for diagnosing infection in these conditions (≈25%) with TTE. When patients meet the modified Duke criteria for probable IE before imaging, TEE is usually the most rational next step for diagnosis.

In certain clinical situations TEE may be preferable as an initial study over TTE, shown in Table 44–3. The American Heart Association (AHA) recommends that TEE be performed in all patients who have a high clinical suspicion for IE and

Table 44–1 Sensitivity and Specificity of Echocardiography in the Diagnosis of Infective Endocarditis

	TTE		TEE	
	Sn	Sp	Sn	Sp
NVE	50-60%	91-98%	92%	91-98%
PVE	17-36%	100%	82-96%	97%
Abscess	28-36%	99%	76-100%	95%

NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; Sn, sensitivity; Sp, specificity.
Data from NVE,[187-191] PVE,[187,192-195] abscess.[189,196,197]

Table 44–2 Clinical Findings Raising Suspicion for IE (Modified from ESC Guidelines)

New murmur or valvular abnormality
Embolism without known origin
Sepsis without known origin
Hematuria, glomerulonephritis, renal infarct
Fever with any of the following:
- Cardiac device or prosthetic valve in place
- Predisposition for IE
- New conduction disturbance
- New congestive heart failure
- Blood cultures growing organism typical for IE
- Multiple or changing pulmonary infiltrates
- Abscess of the kidney, spleen, or spine without clear origin

ESC, European Society of Cardiology; IE, infective endocarditis.
Data from Horstkotte D, Follath F, Gutschik E, et al: Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European Society of Cardiology. Eur Heart J 2004;25: 267-76.

who are at high risk for complications. A decision tree to assist in the initial choice of imaging in the setting of suspected IE is shown in Figure 44–2. If the initial TEE is negative or non-diagnostic, a follow-up study is recommended if IE continues to be suspected 7 to 10 days after the first study.

Echocardiographic images should be interpreted only in conjunction with clinical findings. Examining echocardiographic images in isolation may lead to both false-positive and false-negative results. False-negative studies may result from vegetations smaller than the limits of imaging resolution, recent loss of vegetation that has embolized, or acoustic shadowing from a heavily calcified or prosthetic valve. False-positive studies occur in patients with severe myxomatous valvular disease, ruptured chordae, nonbacterial thrombotic (marantic) endocarditis, Libman-Sacks endocarditis, cardiac tumors, or Lambl's excrescences (small tags that occur on 70% to 90% of adult heart valves).

ANTIBIOTIC THERAPY

The cornerstone of antibiotic therapy is the isolation of the appropriate microorganism. Susceptibility testing helps in the appropriate choice and route of antibiotic therapy. Basic principles of antibiotic therapy include the need for bacteriocidal agents, given for an appropriate duration, and in doses that result in predictable and therapeutic serum levels. Most patients with native valve endocarditis (NVE) are treated with a 4-week course of antibiotics. Patients at higher risk for complications and relapse, such as prosthetic valve endocarditis (PVE), are treated for at least 6 weeks, regardless of whether surgery is performed. In selected patients, such as those with highly sensitive viridans group streptococci or uncomplicated right-sided IE due to methicillin-sensitive *S. aureus* (MSSA), a 2-week course of antibiotic therapy results in high cure rates without substantial recurrence.[2,18,19] In the setting of intravenous drug use (IVDU), the choice of antimicrobial therapy may be tailored on the basis of the type of injected drug. *Staphylococcal* species are the most common pathogens in this patient population. However, users of pentazocine are at risk for *Pseudomonas* infections, while those using brown heroin dissolved in lemon juice are at risk for infection with *Candida* species. Patients with IVDU who also have underlying valvular disease or left-sided IE are at risk for streptococcal and enterococcal infections. Details of recommended antibiotic therapy for the most common infecting organisms in IE are discussed in several reviews and are summarized in Tables 44–4 and 44–5.[2,3,20]

The most common cause of culture-negative IE is prior antimicrobial therapy. In the setting of concurrent antimicrobial therapy, discontinuing antibiotics and waiting for 3 days to draw blood cultures during evaluation for suspected IE is more likely to yield the etiological pathogen. However, in certain situations (e.g., CHF, new conduction abnormalities, embolism) empiric antibiotic therapy should be started without delay. Recommended antibiotic therapy for culture-negative endocarditis is found in Table 44–6.

Table 44–3 Situations When TEE is Preferable to TTE

- Prosthetic valves
- Intracardiac devices (pacemaker, ICD)
- Patients at high risk for complications
  - *Staphylococcus aureus*, fungal infection, prior IE, new heart block, cyanotic congenital heart disease, systemic to pulmonary shunts, poor response to antimicrobials
- Intermediate clinical suspicion of IE
  - Unexplained bacteremia with gram-positive cocci, catheter-associated *S. aureus*, IDU with fever or bacteremia
- Meeting modified criteria for possible IE
- When TTE images are inadequate

IE, infective endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

IDENTIFYING PATIENTS AT RISK FOR COMPLICATIONS OF ENDOCARDITIS

Despite advances in medical and surgical therapy and better diagnostic methods, mortality rates from IE have not significantly changed since 1950. The reason for the lack in improvement in outcomes is related in large part to changes in

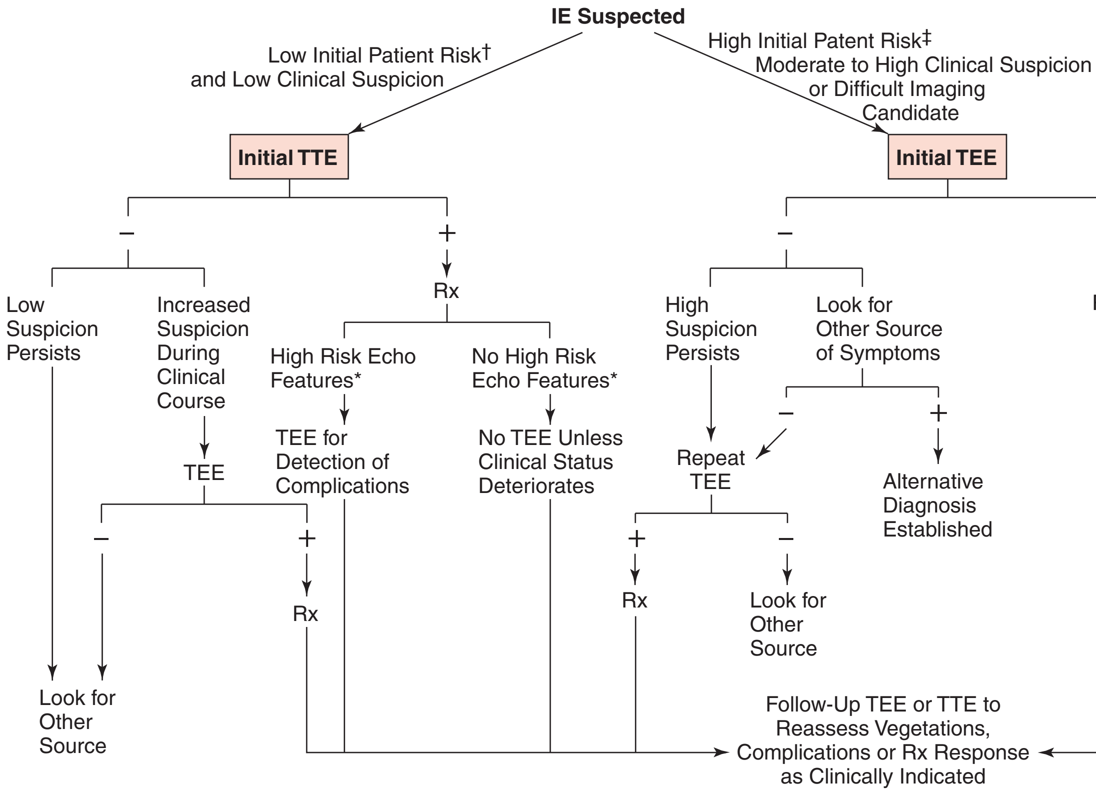

Figure 44–2 An approach to the diagnostic use of echocardiography. *High-risk echocardiographic features include large or mobile vegetations, or both; valvular insufficiency; suggestion of perivalvular extension; or secondary ventricular dysfunction (see text). †For example, a patient with fever and a previously known heart murmur and no other stigmata of IE. ‡High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. Rx indicates antibiotic treatment for endocarditis. (Redrawn from Bayer AS, Bolger AF, Taubert KA, et al: Diagnosis and management of infective endocarditis and its complications. Circulation 1998;98:2936.)

the epidemiology of IE. Paradoxically, medical progress has also contributed to an evolution of the spectrum of IE. With advancements in medical technology, endocarditis is shifting from a subacute to an acute, aggressive disease, increasingly involving the elderly, patients receiving hemodialysis, and those with prosthetic cardiac devices.

The U.S. population is aging, and elderly patients constitute a particularly vulnerable group due to the comorbidities associated with medical illness at an advanced age. The incidence of endocarditis in the elderly is 4 to 9 times greater than in the general population and has increased over the past decade.[21-23] Endocarditis in the elderly is associated with a higher mortality rate ranging from 17% to 28%[24-26] and with a higher risk of complications compared with endocarditis in younger patients. This may be related to a greater incidence of comorbid disease in this population, along with more aggressive pathogens. In at least one study, early surgical therapy in elderly patients with IE was independently associated with a lower in-hospital mortality.[26]

The incidence of IE in patients receiving hemodialysis has also increased over the past decade. Patients with hemodialysis have a fivefold increase in the incidence of valve disease,[27] and the incidence of IE in hemodialysis patients is 50- to 70-fold higher than in the general population.[11,28,29] A trend analysis of the Duke IE Database showed that not only did the overall proportion of IE cases occurring in hemodialysis patients increase over a 10-year period, but also that hemodialysis was the best predictor of *S. aureus* as the infecting microorganism.[30] Because of the more aggressive organisms and underlying comorbid disease, the in-hospital and 1-year death rates are high in hemodialysis patients (23% to 52% and 38% to 75%, respectively).[31-35] Factors associated with worse outcome include age, large vegetations, diabetes as a cause for end-stage renal disease (ESRD), fevers on admission, elevated WBC, multivalve IE, mitral annular calcification or severe mitral regurgitation in the setting of mitral valve IE, severe aortic regurgitation in the setting of aortic valve IE, and negative blood cultures.[31,32,34,35] When treating patients medically, one is tempted to use vancomycin even for MSSA because of its ease of administration in the hemodialysis patient. However, vancomycin exerts only a slow bactericidal effect and is less active than β-lactams for MSSA. In addition, there is justifiable concern that overuse of this agent will lead to emergence of vancomycin-resistant microorganisms. When a tunneled or other central catheter is in place, every effort should be taken to remove the catheter because cure is unlikely when catheter salvage is attempted.[36] In a single-center study, valve surgery was found to be an adverse predictor of outcome (75% mortality vs. 40% treated medically), raising concern about using traditional recommendations for surgery in patients receiving hemodialysis.[34]

Although diabetes mellitus is associated with an adverse prognosis in the hemodialysis population, the impact on the mortality rate in patients without end-stage kidney disease is

Table 44–4 Recommended Antimicrobial Therapy for Common Microorganisms in Infective Endocarditis

Microorganism	Native Valve	Prosthetic Valve	Notes
PCN-susceptible viridans streptococci and *S. bovis*, MIC ≤ 0.12 mcg/mL	PCN G 12-18 million U/24 hr IV continuously or in 4-6 divided doses × 4 wk *or* Ceftriaxone 2 g/24 hr IV/IM in 1 dose × 4 wk *or* Vancomycin 30 mg/kg/24 hr IV in 2 divided doses (not to exceed 2 g/24 hr) × 4 wk	PCN G 24 million U/24 hr IV continuously or in 4-6 divided doses × 6 wk *or* Ceftriaxone 2 g/24 hr IV/IM in 1 dose × 6 wk *with or without* Gentamicin 3 mg/kg/24 hr IV/IM in 1 dose × 2 wk *or* Vancomycin 30 mg/kg/24 hr IV in 2 divided doses (not to exceed 2 g/24 hr) × 6 wk	2-wk course of PCN G + gent (3 mg/kg/24 hr in one dose) or ceftriaxone + gent (3 mg/kg/24 hr in one dose) alternative in uncomplicated native valve cases in patients at low risk for gentamicin toxicity. Vancomycin only for patients unable to tolerate PCN or ceftriaxone.
Relative PCN-resistant viridans streptococci and *S. bovis*, MIC > 0.12 mcg/mL and ≤ 0.5 mcg/mL	PCN G 24 million U/24 hr IV continuously or in 4-6 divided doses × 4 wk *or* Ceftriaxone 2 g/24 hr IV/IM in 1 dose × 4 wk *plus* gentamicin 3 mg/kg 24 hr IV/IM in one dose × 2 wk *or* Vancomycin 30 mg/kg/24 hr IV in 2 divided doses (not to exceed 2 g/24 hr)	PCN G 24 million U/24h IV continuously or in 4-6 divided doses x 6 wks *or* Cetriaxone 2 g/24 hr IV/IM in 1 dose × 6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 1 dose × 6 wk *or* Vancomycin 30 mg/kg/24 hr IV in 2 divided doses (not to exceed 2 g/24 h) × 6 wk	MIC > 0.5 mcg/mL strains treated with regimen recommended for enterococcal endocarditis later. Vancomycin only for patients unable to tolerate PCN or ceftriaxone.
Oxacillin-susceptible staphylococci	Nafcillin or Oxacillin 12 g/24 hr IV in 4-6 divided doses × 6 wk *with (optional)* Gentamicin 3 mg/kg/24 hr IV/IM in 2 or 3 divided doses × 3-5 days	Nafcillin or Oxacillin 12 g/24 hr IV in 6 divided doses ≥ 6 wk *with* Rifampin 900 mg/24 hr IV/po in 3 divided doses ≥ 6 wk *with* Gentamicin 3 mg/kg/24 hr IV/IM in 2 or 3 divided doses × 2 wk	For uncomplicated right-sided IE 2-wk course of nafcillin or oxacillin with gentamicin 3 mg/kg/24 hr in 2-3 divided doses. If history of non–anaphylactoid-type hypersensitivity reactions to β-lactams Cefazolin 6 g/24 hr IV in 3 divided doses × 6 wk *with (optional)* Gentamicin 3 mg/kg/24 hr IV/IM in 2 or 3 divided doses × 3-5 days. If history of anaphylactoid-type hypersensitivity to β-lactams, vancomycin should be used (based on oxacillin-resistant protocol).
Oxacillin-resistant staphylococci	Vancomycin 30 mg/kg/24 hr IV in 2 divided doses × 6 wk	Vancomycin 30 mg/kg/24 hr IV in 2 divided doses ≥ 6 wk *with* Rifampin 900 mg/24 hr IV/po in 3 divided doses ≥ 6 wk *with* Gentamicin 3 mg/kg/24 hr IV/IM in 2 or 3 divided doses × 2 wk	

Continued

Table 44–4 Recommended Antimicrobial Therapy for Common Microorganisms in Infective Endocarditis—cont'd

Microorganism	Native Valve	Prosthetic Valve	Notes
HACEK Microorganisms (*Hemophilus parainfluenzae*, *H. aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*)	Ceftriaxone 2 g/24 hr IV/IM in one dose × 4 wk or Ampicillin-sulbactam 12 g/24 hr IV in 4 divided doses × 4 wk or Ciprofloxacin 1000 mg/24 hr po or 800 mg/24 hr IV in 2 divided doses × 4 wk	Same protocol as native valve HACEK infection but for 6-wk course	May substitute cefotaxime or another third- or fourth-generation cephalosporin Fluoroquinolone therapy recommended only for patients intolerant to cephalosporins and ampicillin.

Vancomycin dose should be adjusted to obtain a peak 1 hr after infusion completed of 30-45 mcg/mL, and a trough of 10-14 mcg/mL. Dose of greater than 2 g/24 hr acceptable if serum concentrations inappropriately low.
Gentamicin dose should be adjusted to obtain peak of 3-4 mcg/mL and trough < 1 mcg/mL when 3 divided doses are used.
Nomogram used for single daily dosing.
See reference for pediatric dosing.
PCN, penicillin.
Data modified from references 200-202.

less clear. Chu and associates[37] found that diabetes, *S. aureus*, and embolic events were independently associated with adverse outcomes after controlling for severity of illness in a large prospectively collected population cohort. In contrast, others have not found diabetes to predict outcomes,[38,39] although these studies have been limited by retrospective identification and collection of cases, small sample size, and single center experiences.

Injection drug use has emerged as an important risk factor for IE, with incidences in this group of 720/100,000 person years[40] compared with 2.4 to 5.9/100,000 person years in the general population.[41,42] In HIV-positive patients, IE is uncommon in the absence of IVDU.[43] However, the combination of HIV and IVDU is associated with an even greater risk for developing IE.[40,44] Patients with IVDU more commonly have right-sided IE, which is associated with a low (<5%) hospital mortality rate.[45] However, left-sided IE in these patients has a mortality rate of 20% to 30%.[45] The presence of HIV itself is not associated with an adverse prognosis from IE,[46] although CD4 levels < 200 are associated with higher mortality rates.[47]

MANAGEMENT OF COMPLICATED INFECTIVE ENDOCARDITIS

Congestive Heart Failure

Congestive heart failure (CHF) is the most common cause of death in IE. The most common cause of CHF is infection-related valvular dysfunction. Endocarditis complicated by acute aortic insufficiency (AI) is associated with particularly high risk because acute AI is poorly tolerated and results in rapid progression of CHF in most cases.[48] The risk of CHF is also increased in the presence of virulent pathogens, such as *S. aureus;* hemolytic streptococci groups A-C, F, and G; and *Streptococcus pneumoniae.*[49]

Heart failure is the most common and accepted indication for surgery. It is the primary indication for surgery in 22% to 71% of cases of surgically treated IE.[50,51] Heart failure carries a worse prognosis with medical therapy alone, but it also increases surgical risks. Operative mortality for IE ranges from 6% to 11% in the absence of CHF compared with 11% to 35% when CHF has developed.[3,48,52] Four observational studies from the 1970s and 1980s compared combined medical and surgical therapy with medical therapy alone in the treatment of IE complicated by CHF and they found mortality rate with surgery ranged from 11% to 35% compared with 56% to 86% with medication alone.[53-56] In more contemporary series the mortality for surgically treated patients with decompensated CHF is 10% versus 20% to 27% in patients treated conservatively.[49,57] Significant treatment bias exists in all of the aforementioned observational studies. For instance, patients selected for surgery may be more acutely ill; conversely, patients who may require surgery can be denied this therapy because of advanced age and other comorbid diseases. Although there are no randomized trials comparing surgical with medical therapy for IE complicated by CHF, the most compelling evidence for the benefit of surgery comes from Vikram and associates.[58] By using propensity scores to reduce selection bias, they concluded that patients with moderate-to-severe CHF had a significant reduction in mortality with surgery compared with conservative therapy (HR 0.22, CI 0.08 to 0.53).[58] In fact, in this study the only group of patients in which surgery appeared to confer a survival advantage was that group with moderate-to-severe CHF.

Surgery should be performed before intractable CHF develops. Postoperative mortality is proportional to the severity of hemodynamic impairment at the time of surgery.[59] The mortality benefit is most apparent when surgery is performed early in the course of disease.[57] There is no evidence that delaying surgery to give additional antibiotics improves outcome. The small (2% to 7%) potential risk of recurrent IE

Table 44–5 Recommended Antimicrobial Therapy for Enterococcal Infective Endocarditis

Microorganism	Native or Prosthetic Valve	Notes
Enterococcus susceptible to PCN, gentamicin, and vancomycin	Ampicillin 12 g/24 hr IV in 6 divided doses *or* PCN G 18-30 million U/24 hr IV continuously or in 6 divided doses × 4-6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 4-6 wk *or* Vancomycin 30 mg/kg/24 hr in 2 divided doses × 6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 6 wk	Native valve: 4-wk dual therapy if ≤ 3 mo of symptoms; 6-wk dual therapy if > 3 mo of symptoms. Prosthetic valve: minimum 6 wk of dual therapy. Vancomycin only for patients intolerant to penicillin or ampicillin.
Enterococcus susceptible to PCN, streptomycin, and vancomycin and resistant to gentamicin	Ampicillin 12 g/24 hr IV in 6 divided doses *or* PCN G 24 million U/24 hr IV continuously or in 6 divided doses × 4-6 wk *plus* Streptomycin 15 mg/kg/24 hr IV/IM in 2 divided doses × 4-6 wk *or* Vancomycin 30 mg/kg/24 hr in 2 divided doses × 6 wk *plus* Streptomycin 15 mg/kg/24 hr IV/IM in 2 divided doses × 6 wk	Native valve: 4-wk dual therapy if ≤ 3 mo of symptoms; 6-wk therapy if > 3 mo of symptoms. Prosthetic valve: minimum 6 wk of dual therapy. Vancomycin only for patients intolerant to penicillin or ampicillin.
Enterococcus resistant to PCN and susceptible to aminoglycoside and vancomycin	Ampicillin-sulbactam 12 g/24 hr IV in 4 divided doses × 6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 6 wk *or* Vancomycin 30 mg/kg/24 hr IV in 2 divided doses × 6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 6 wk	If strain gentamicin resistant, > 6 wk of ampicillin-sulbactam required. Vancomycin only for patients intolerant to ampicillin-sulbactam. If intrinsic penicillin resistance, use vancomycin plus gentamicin dosing; consultation with infectious disease specialist recommended.
Enterococcus resistant to PCN, aminoglycoside, and vancomycin	*E. faecium*: Linezolid 1200 mg/24 hr IV/PO in 2 divided doses ≥ 8 wk *or* Quinupristin-dalfopristin 22.5 mg/kg/24 hr IV in 3 divided doses ≥ 8 wk *E. faecalis*: Imipenem/cilastin 2 g/24 hr IV in 4 divided doses ≥ 8 wk *plus* Ampicillin 12 g/24 hr IV in 6 divided doses ≥ 8 wk *or* Ceftriaxone 4 g/24 hr IV/IM in 2 divided doses *plus* Ampicillin 12 g/24 hr IV in 6 divided doses ≥ 8 wk	Consultation with infectious disease specialist recommended. Cure with antibiotics alone < 50%; valve replacement may be needed for cure.

Vancomycin dose should be adjusted to obtain a peak 1 hour after infusion completed of 30-45 mcg/mL and a trough of 10-14 mcg/mL. Dose of greater than 2 g/24 hr acceptable if serum concentrations inappropriately low.
Gentamicin dose should be adjusted to obtain peak of 3-4 mcg/mL and trough < 1 mcg/mL when 3 divided doses are used. Nomogram used for single daily dosing.
See reference for pediatric dosing.
PCN, penicillin.
Data modified from references 200-202.

Table 44–6 Recommended Antimicrobial Therapy for Culture-negative Infective Endocarditis Including *Bartonella*

	Native Valve	Prosthetic Valve	Notes
Culture-negative endocarditis	Ampicillin-sulbactam 12 g/24 hr IV in 4 divided doses × 4-6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 4-6 wk *or* Vancomycin 30 mg/kg/24 hr IV in 2 divided doses × 4-6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 4-6 wk *plus* Ciprofloxacin 1000 mg/24 hr PO or 800 mg/24 hr IV in 2 divided doses × 4-6 wk	**Early ≤1 yr** Vancomycin 30 mg/kg/24 hr IV in 2 divided doses × 6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 2 wk *plus* Cefepime 6 g/24 hr in 3 divided doses × 6 wk *plus* Rifampin 900 mg/24 hr PO/IV in 3 divided doses × 6 wk **Late > 1 yr** Same regimen as listed for culture-negative native valve IE with the addition of rifampin	Consultation with an infectious disease specialist recommended. Vancomycin only for patients unable to tolerate penicillins.
Suspected *Bartonella*, culture negative	Ceftriaxone 2 g/24 hr IV/IM in 1 dose × 6 wk *plus* Gentamicin 3 mg/kg/24 hr IV/IM in 3 divided doses × 2 wk *with or without* Doxycycline 200 mg/ 24 hr IV/PO in 2 divided doses × 6 wk	Same regimen as listed for culture-negative native valve IE	Consultation with an infectious disease specialist recommended
Documented *Bartonella*, culture negative	Doxycycline 200 mg/ 24 hr IV/PO in 2 divided doses × 6 wk *plus* Gentamicin 3 mg/kg/ 24 hr IV/IM in 3 divided doses × 2 wk		Consultation with an infectious disease specialist recommended Use rifampin 600 mg/24 hr PO/IV in 2 divided doses if gentamicin cannot be given.

Vancomycin dose should be adjusted to obtain a peak 1 hr after infusion completed of 30-45 mcg/mL and a trough of 10-14 mcg/mL. Dose of greater than 2 g/24 hr acceptable if serum concentrations inappropriately low.
Gentamicin dose should be adjusted to obtain peak of 3-4 mcg/mL and trough < 1 mcg/mL when 3 divided doses are used. Nomogram used for single daily dosing.
See reference for pediatric dosing.
Data modified from references 200-202.

after surgery in the acute phase is far less than the mortality rate from uncontrolled CHF.[60-62]

Abscess

Extension beyond the leaflets occurs in 8% to 40% of NVE,[63-66] most commonly in the aortic annular region, and has been reported in 56% to 100% of patients with PVE.[54,66-69] Periannular invasion is more common in bioprosthetic valves during the first postoperative year compared with later, while invasive disease occurs in mechanical valves regardless of time from implantation.[70]

Significant predictors of abscess include aortic valve involvement, IV drug use, and new atrioventricular (AV) or bundle branch block.[66,71,72] The development of new AV or bundle branch block has a positive predictive value of 77% but a relatively low sensitivity (42%) for abscess formation.[66] The presence of intraventricular block (bundle branch or hemiblock) also has poor prognostic implications, with mortality rates of 31% compared with 15% in patients without block.[73] Periannular extension is more common in patients with *S. aureus* IE[74] and should be suspected in patients with NVE with uncontrolled infection or acute hemodynamic deterioration. All patients with PVE involving the aortic valve are at high risk for abscess and should be evaluated aggressively.

Delivery of antibiotics to extravalvular tissue is difficult, and for this reason the mortality rate of medically treated patients with abscess may reach 75% or higher.[74-76] As a result, surgical therapy is preferred in most cases of abscess forma-

tion, with operative mortality rates in many,[77,78] but not all, series[59] not significantly different from patients operated on without abscess. If the surgical procedure is radical, resulting in complete resection of the abscess cavity and restoration of near-normal hemodynamics, presurgical abscess is not a predictor of early surgical mortality or reinfection rate.[79] A small number of patients with abscesses may be treated medically provided they are followed by serial TEE for progression of disease. Contraindications for medical management include heart block, valvular regurgitation, and dehiscence. If any of these conditions occur during medical management, prompt surgical intervention should be pursued.[80]

Embolic Events

The incidence of clinically significant embolic events ranges from 22% to 50%[81-86] and, in prospective targeted evaluations, is closer to 50%.[87] Stroke represents 50% to 65% of these cases and is a major contributor to the morbidity and mortality rates associated with IE.[88] The majority of strokes are diagnosed before antibiotic treatment begins.[88,89] Most "preventable strokes," defined as those occurring after the initiation of treatment, occur early. The frequency of embolism dramatically declines after initiation of antibiotic therapy.[49]

Vegetation size, morphology, and location have been associated with embolic risk. In a meta-analysis of 10 studies involving a total of 738 patients, 37% of the 323 patients with vegetations > 10 mm in diameter experienced embolism, a risk almost 3 times greater than in patients with smaller vegetations.[90] Some investigators found large vegetations independently predicted embolic events only in viridans group streptococcus, whereas infections with *S. aureus* had a high risk of embolism regardless of vegetation size.[81,83]

Evidence indicates that vegetations on the mitral valve (particularly the anterior leaflet) are associated with the highest risk for embolism and stroke (21% to 32% with mitral valve IE vs. 11% to 15% with aortic valve IE).[11,89] The degree of vegetation mobility may also predict embolic risk.[83,91] When the incidences of both silent emboli (as assessed by cerebral and thoracoabdominal CT scans) and clinically apparent emboli are included, the rate of embolic events is particularly high (83%) in the setting of vegetations that are large (>15 mm) and mobile.[83]

Developing risk models that allow appropriate stratification of patients with endocarditis is important. Clinical risk factors that increase the risk for embolization are shown in Table 44–7. Novel factors that may influence risk include circulating adhesion molecules, which may be stronger predictors of thromboembolism in endocarditis than echocardiographic features.[92] In addition, coagulation parameters, antiphospholipid antibodies, and endothelial cell activation have also been associated with thromboembolic events.[93] Elevation in serum CRP levels also appears to be associated with major embolic events,[86] and there is evidence that CRP plays a role in activating the coagulation cascade by inducing monocyte production of tissue factor.[94] Identifying risk factors associated with embolism may be useful in selecting patients who might benefit from early surgical therapy.

Although current practice suggests that surgery be performed after 2 or more embolic events occur on antibiotic therapy, many experts advocate earlier surgical intervention; however, evidence to support this position is limited. If the patient has another indication for surgical therapy, such as significant valvular regurgitation or CHF, the decision is easier because surgery will achieve a twofold objective. Likewise, surgery may be considered following a single embolic episode in patients with a persistent vegetation when the risk of repeat embolism, based on clinical, microbiologic, or echocardiographic parameters, is believed to be high. Whether surgery is warranted in the presence of a large mobile vegetation without evidence of embolism is unclear. However, when the goal is to prevent embolic events, surgery is best performed early because the rate of embolism decreases significantly after the first 1 to 2 weeks of medical treatment.[86]

Table 44–7 Risk Factors for Stroke/Embolism

Clinical	Microbiology	Echocardiography
Prior embolism Short symptom duration Older age PVE Atrial fibrillation	*S. aureus* *Candida* species Abiotrophia HACEK	MV infection Perivalvular extension Increase in size during Rx Vegetation number mobility size > 10 mm

Mycotic Aneurysms

Occurring in 1.2% to 5% of IE, mycotic aneurysms (MAs) result from embolization to the vasa vasorum with spread of infection into the intima and through the vessel wall.[95,96] They are associated with an increased mortality rate that ranges from 30% for unruptured to 80% for ruptured aneurysms.[97] The most common location is in the branch points of cerebral arteries, but visceral arteries and arteries of the extremities may also be involved. In the absence of signs or symptoms, routine screening for MA is not indicated. When symptoms that suggest MA are present (focal neurologic deficits or localized severe headaches), an MRI is often performed as the initial step. However, angiography is the diagnostic procedure of choice.[95]

Once the diagnosis of an intracranial MA is established, monitoring with serial angiograms is recommended, with prompt repair if the aneurysm is enlarging in size or is bleeding. Endovascular therapy is less invasive and is a viable alternative to surgical clipping or ligation. Intracranial MAs will often heal with medical therapy. However, extracranial mycotic aneurysms usually rupture if left untreated and preemptive repair is recommended. The diagnosis is often an incidental finding; for example, symptoms of extracranial MA rupturing include massive diarrhea (rupture of an MA into the bowel) or hematuria and increased blood pressure (rupture of a renal MA).

Prosthetic Valve Infections

Prosthetic valve IE can be devastating. The increased frequency of paravalvular invasion, particularly in early PVE, results in a greater incidence of complications such as heart failure, persistent fever, or new conduction abnormalities when compared with NVE. The reported mortality rates for PVE range

from 5% to 69%, with most studies suggesting a rate of 20% to 30%.[12,98-106] Early PVE (defined as occurring within the first postoperative year) is associated with a particularly high mortality rate[12] and is more likely to be associated with paravalvular invasion and hemodynamically significant valvular lesions.

The frequency of PVE is highest during the initial 3 months following implantation, remains high through the sixth month, and declines gradually to a relatively constant rate of 0.3% to 0.8% per year at 12 months and thereafter.[107-109] The infection risk may be higher for mechanical valves during the initial year following implantation, but over time the risk of infection for a bioprosthetic valve increases such that there is no overall difference in infection rates between the two valve types 5 years postoperatively.[108,109] Patients with prosthetic valves who develop nosocomial bacteremia are at high risk for developing PVE, with an incidence rate of 11%.[110]

The use of anticoagulation therapy is controversial. Experts agree that there is no role for the introduction of anticoagulation for patients who otherwise do not require it. Most experienced clinicians continue administration of anticoagulation during therapy for mechanical valve IE. This approach has been questioned, particularly in patient populations who are at high risk for embolism (e.g., *S. aureus* infection) during the first 1 to 2 weeks of therapy.[111] In patients with *S. aureus* PVE with embolism, discontinuation of anticoagulation for a period of 2 weeks is recommended.[20] Although aspirin has been shown to reduce vegetation size and embolism in some animal models, a randomized clinical trial did not show any reduction in embolization in patients receiving aspirin therapy. Notably, in that trial patients receiving aspirin therapy had a high rate of bleeding complications.[112] Therefore, the routine use of aspirin is not recommended for the purpose of preventing embolic events.[20]

Certain clinical findings help to identify patients who are at high risk for complications and death when they are treated with medical therapy alone. Patients who develop any of the following are at high risk for significant complications (including death) and unlikely to respond to medical therapy alone: pathologic murmurs or moderate-to-severe heart failure as a result of valve dysfunction, fever more than 10 days despite appropriate medical therapy, new-onset heart block, or echocardiographic evidence of abscess or valve dehiscence.[113,114] The addition of surgery to the treatment plan for high-risk patients results in greater survival rates, fewer relapses, and fewer rehospitalizations for valve surgery.[113,115,116] *S. aureus* PVE is associated with a particularly grave prognosis, with the mortality rate ranging from 28% to 82%.[113,114,117-119] Surgery appears to improve outcomes in *S. aureus* IE, regardless of the presence of cardiac complications.[117] Indications for surgical therapy of PVE are not absolute and should be implemented with careful attention to the relative risks and benefits for a given patient. For instance, there is observational evidence that supports medical therapy alone for patients with late-onset PVE caused by viridans streptococci, HACEK group, or enterococci without evidence of paravalvular invasion or valve dysfunction.[120] If medical therapy alone is pursued, frequent follow-up is required.

Table 44–8 Indications for Surgical Therapy

Moderate to severe CHF due to valve dysfunction
Extension of infection into adjacent structures
Fistula formation
Rupture into pericardium
New conduction disturbance
Abscess
Unstable prosthesis in PVE
Persistent bacteremia or fever despite appropriate antimicrobial therapy
No available effective antibiotic treatment
NVE with difficult to treat organisms
Coxiella burnetii, Brucella, left-sided *Pseudomonas aeruginosa*, fungal infections
PVE caused by *S. aureus*, multidrug resistant enterococci, fungi, *Pseudomonas* aeruginosa, *Brucella* species, *Coxiella burnetii*
Destructive microorganisms (*S. lugdunensis*)
Culture-negative PVE with unexplained fever > 10 days duration
PVE with relapse despite optimal therapy
Very large (>10 mm), very mobile vegetations
Increasing size of vegetation on antimicrobial therapy
Large (>20 mm) vegetation on tricuspid valve with septic pulmonary emboli

Data from references 203-208.

WHEN TO REFER FOR SURGICAL THERAPY

Surgical therapy is required during the early phase of IE in 20% to 40% of patients overall and in an even greater percentage of cases of patients with mitral valve IE.[42,49,60,98,121,122] Published experiences of surgery during active IE show operative mortality rates ranging from 5% to 16%, with actuarial 5- and 10-year survival rates of 75% and 61%, respectively.[48,50,51,57,59,79,121,123] By comparison, mortality rates for the same operative procedures are lower when performed for reasons other than IE.[50,121] Commonly accepted indications for surgery are shown in Table 44–8.

The decision for surgical therapy should not be based on absolute indications but rather on serial clinical evaluations, microbiologic results (including surveillance blood cultures on appropriate therapy), and echocardiographic findings (Fig. 44–3). Treatment failure should generally not be assumed unless (1) fever persists for more than 7 days or (2) blood cultures remain positive after 7 days of appropriate antibiotic therapy and a search for metastatic infection is negative.

Results of surgery depend on many factors including the preoperative condition of the patient, timing of the surgery, surgical techniques, and postoperative management. Preoperative predictors of mortality include NYHA classification, age, and the presence of renal failure.[51,57,59,79,123,124] Aggressive disease of a shorter duration, as occurs with *S. aureus,* is also associated with increased mortality.[23]

Early surgical intervention in the acute phase, particularly in the presence of uncontrolled infection, may seem risky due to concerns about placing prosthetic material into a highly infected field with the potential for failure and recurrence of IE. Some investigators have reported that surgical inter-

vention during the acute phase of IE was associated with increased risk for persistent or early recurrent PVE.[50,118,125] In contrast, others did not find this to be true,[60,62,119,126,127] particularly for mitral valve disease.[118,121] With increasing experience and good results, there is a trend for earlier operation in patients with IE. The final surgical outcome appears to have little relation to the duration and intensity of antibiotic therapy before surgery.[57,59,60,123,128-130] However, it is important that adequate bactericidal concentrations of antibiotics be present to kill bacteria entering the circulation during surgical débridement. In general, when surgery is indicated, prognosis is improved if surgery is performed early before the general condition of the patient has deteriorated.[60,68,98]

No randomized trials have shown a benefit with surgical therapy. When patients who undergo surgery are carefully matched using propensity scoring to reduce treatment bias, surgery in a diverse group of patients with IE is associated with a 50% reduction in the 6-month mortality rate versus medical therapy alone, although almost all of this benefit occurred in patients who had moderate-to-severe CHF.[58]

All patients with neurologic symptoms should undergo CT of the brain to clarify the nature and extent of disease and to identify hemorrhage before they undergo surgical therapy for IE. Cerebral angiography is recommended for patients with CT evidence of hemorrhage because 10% to 50% of these patients will have a ruptured MA.[131,132] A ruptured MA should be resected, clipped, or embolized before valve surgery occurs.[131]

After a stroke has occurred, the patient's risk for possible further neurologic damage during cardiopulmonary bypass becomes a concern. Some authors assert that valve replacement can be performed 72 hours or later after an ischemic cerebral infarct with a low risk of perioperative stroke in the absence of hemorrhage.[133] However, in a multicenter retrospective study involving 181 patients with cerebral complications, who underwent surgery for IE, the risk for exacerbation of neurologic events persisted for weeks.[134] This risk decreased with time regardless of the type of stroke; 15 and 28 days after stroke, the rates of exacerbation were 10% and 2.3%, respectively. Most investigators recommend allowing a 2- to 3-week interval between neurologic events and the cardiac operation.[131,135]

The choice of surgical technique plays a role in short- and long-term outcomes. Mitral valve repair and the use of homografts in the aortic position, even in the presence of active infection, may reduce the incidence of infective recurrence.[51,67,136,137] In the setting of mitral valve IE, valve repair should be performed whenever possible because it is associated with a lower mortality rate (0% to 9%) compared with mitral valve replacement (5% to 25%) and low rates of

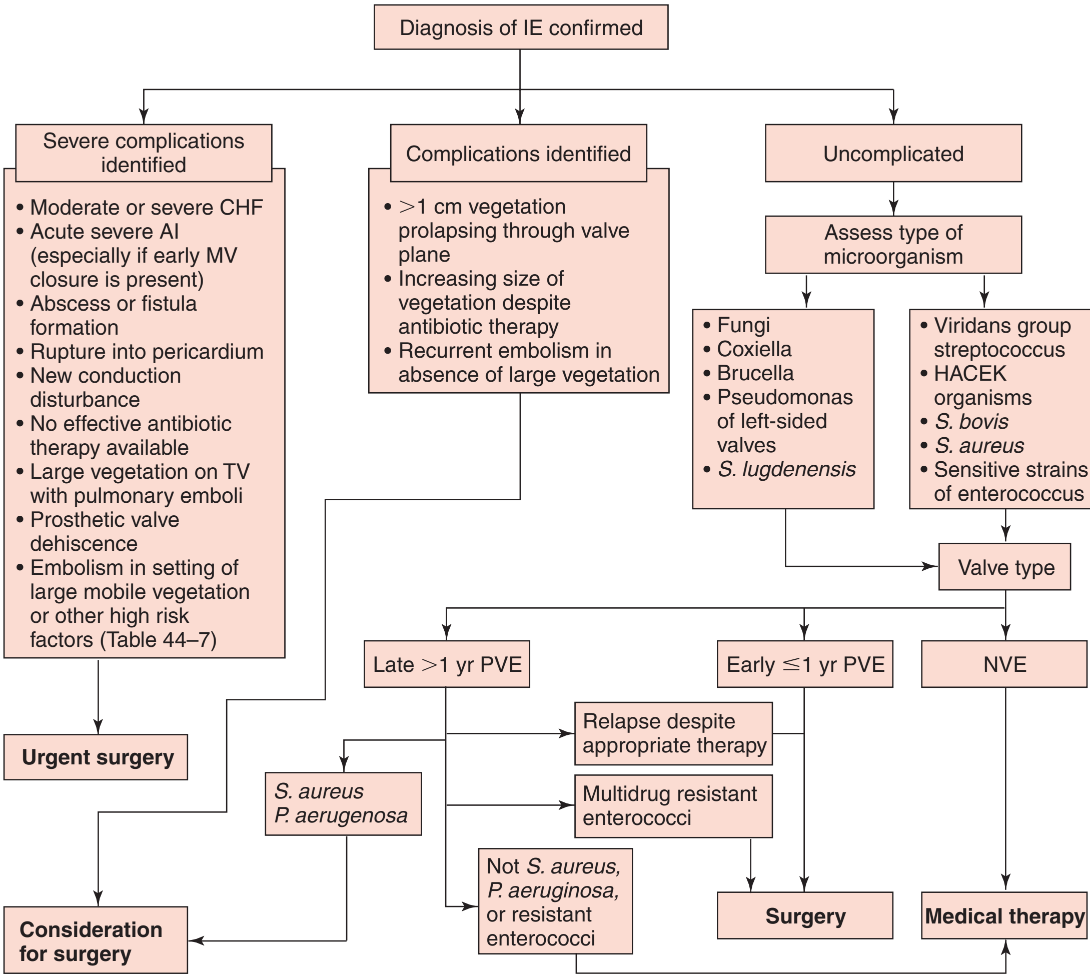

Figure 44–3 Decision tree for surgical therapy.

recurrent infection.[68,138-141] Ten-year survival rates in the setting of mitral valve repair are 80%,[141] compared with 61% after mitral valve replacement.[59]

For aortic valve IE, homograft replacement may be a better option in terms of reducing recurrent IE.[51] Homografts are also an advantage in the setting of extensive periannular destruction by infection.[137,142,143]

DEVICE-RELATED INFECTIONS

Cardiac device-related infections (CDIs) are becoming increasingly important because they represent a leading cause of death and disability after device implantation. The published incidence varies from 0.6% to 5.6% in recent series,[144-147] with 10% to 15% of all CDIs having involvement of an intracardiac lead. The risk of pacemaker-associated infection among high-risk populations, such as those with *S. aureus* bacteremia, may be as high as 45%.[148] Reported internal cardiac defibrillator (ICD) infection rates, although not studied systematically, appear to be at least 0.8% to 1.5% in nonthoracotomy devices.[144,145,149] The past decade has seen an exponential increase in placement of cardiac devices. In the Medicare population, CDIs have outpaced the increase in implantations, with an increase from 0.94 to 2.11 infections per 1000. Medicare beneficiaries have experienced a 124% relative increase, which may represent both an increase in the absolute number of patients with intracardiac devices, as well as an increase in the at-risk years for those patients.[150]

With contemporary data expanding the indications for defibrillators and biventricular pacemakers,[151-154] rates of device infections can be expected to keep increasing. The importance of CDI is further underscored when one considers that the cost of standard therapy includes removal of the entire device; intravenous antibiotics; and, in most instances, reimplantation of the device.[155]

TEE outperforms TTE in the detection of device IE and has a high concordance with surgical findings. The sensitivity of TTE ranges from 22% to 30% versus 95% for TEE.[147,156,157] Once a device infection is confirmed, a total of 4 to 6 weeks of appropriate antibiotic therapy is recommended on the basis of microorganism susceptibilities. *Staphylococcus epidermidis* and *S. aureus* are the most common infecting organisms,[147,155,157,158] and empiric therapy should be based accordingly on coverage. Because of unacceptably high relapse and death rates in patients whose device removal was incomplete, it is recommended that, in addition to antibiotic therapy, complete system removal be performed.[147,155] Removal can be performed using excimer laser with a complete extraction success rate of 95%.[159] Percutaneous removal has been described even for patients with large vegetations and is associated with a low complication rate.[156,160] We recommend an echocardiogram with contrast before percutaneous removal of an intracardiac lead to rule out a right-to-left cardiac shunt, particularly when large vegetation is evident. At the time of device removal, cultures from the device pocket and from all lead tips and mesh should be performed. Surgical removal is required in the setting of epicardial leads or in the presence of a right-to-left shunt and may be considered in the setting of a large mobile vegetation on the lead. In pacemaker-dependent patients, temporary pacing will be required, with leads placed on the ipsilateral side of infection proximal to the infected site.[161] Most authors recommend waiting at least 7 to 10 days before device replacement, after serial blood cultures are sterile and signs of infection are absent.

Preventive measures can reduce cardiac device infections. Preimplantation fever, the use of a temporary pacing wire before implantation, and early reintervention increase the risk for infection.[162]

Infections are often acquired at the time of device placement or during subsequent manipulation and are often latent. A meta-analysis of antibiotic prophylaxis before pacer placement in 2023 patients who were randomized to antibiotics versus placebo showed a consistent protective effect that decreased subsequent pocket and pacemaker infections by a magnitude of 40 over a mean follow-up of 2 years.[163]

LONG-TERM OUTCOMES—MANAGEMENT OF HOSPITAL SURVIVORS

Patients who survive the initial hospitalization are subject to long-term complications that are related to the predisposing factors that led to the initial infection, new valvular damage, or the prosthetic heart valve placed during the initial hospitalization. Relapse, defined as resumption of IE within 6 months of treatment with the same microorganism, occurs in approximately 3% of patients.[119,127,164] Recurrence, infection with a different organism, or infection more than 6 months after the initial episode occurs in 2.5% to 12.3% of hospital survivors.[12,119,164-166] The probability of recurrence-free survival is lower in men and in the elderly.

Between 19.7% and 47% of patients with IE who are treated medically will eventually require valve replacement, most frequently in the first 2 years of follow-up.[119,127,164,167] Patients who receive valve replacements during the acute episode of IE or during the follow-up period are at risk for all the complications that are associated with prosthetic heart valves including valve degeneration, thromboembolic events, bleeding, and recurrent infection.[168] In published series, the long-term mortality rate in hospital survivors varies greatly, most reporting a 10-year survival rate from 48% to 80%.[50,121,127,140,169] Age and recurrent endocarditis are significant predictors of mortality in the follow-up period.[164]

After the patient has completed the antibiotic course, any indwelling lines used for therapy should be removed promptly.[20] Surveillance blood cultures should be performed 5 to 7 days after discontinuation of antibiotics to confirm the effectiveness of therapy. A repeat TTE should be obtained after therapy to document the extent of residual valvular abnormalities and to reestablish baseline hemodynamics after valve repair or replacement surgery. The patients should be educated regarding antibiotic prophylaxis because they represent a high-risk group for recurrent IE. In addition, the patient should be referred for dental treatment if necessary. He or she should be scheduled for regular follow-up to assess for CHF and evidence for progression of valve disease.[20]

PREVENTION

Historically, endocarditis has been a disease associated with underlying valvular abnormalities, particularly rheumatic

Table 44–9 Underlying Cardiac Disease at Risk for Adverse Outcomes in Setting of IE

High Risk	Moderate Risk
Prosthetic valves	Most other congenital heart disease (excluding secundum ASD)
Prior IE	Acquired valvular heart disease
Cyanotic congenital heart disease	Hypertrophic obstructive cardiomyopathy
Surgically constructed systemic to pulmonary shunts	MVP with thickened leaflets or regurgitation

ASD, atrial septal defect; IE, infective endocarditis; MVP, mitral valve prolapse.

heart disease, and with community-acquired bacteremia. Approximately two thirds (53% to 70%) of patients with endocarditis have preexisting cardiac disease.[11,49,170] Few studies have quantified the actual risk for the development of IE on the basis of predisposing cardiac risk factors. Therefore, organizations such as the American Heart Association (AHA) and the European Society of Cardiology (ESC) base their recommendations for prophylaxis not only on the risk for the development of IE, but also on the risk for an adverse outcome if IE were to occur (Table 44–9*).* Patients with acquired valvular dysfunction are said to be at moderate risk for IE, although guidelines for antibiotic prophylaxis are not specific about which valvular abnormalities are included in this entity. Some authors have suggested using the U.S. Department of Health and Human Services (DHHS) criteria for valvular abnormalities: moderate or greater mitral, tricuspid, or pulmonary regurgitation; mild or greater aortic regurgitation; mild or greater mitral regurgitation with a thickened or redundant mitral valve; and any valvular stenosis of mild or greater degree.[171]

Because there have been no randomized, controlled trials in humans with underlying heart disease to determine whether antibiotic administration prevents IE, there has been controversy regarding the effectiveness of antibiotic prophylaxis for prevention of IE. Therefore, recommendations are based on in vitro susceptibilities of microorganisms known to cause IE, as well as on animal models of endocarditis. Four small case control studies have focused on antibiotic prophylaxis: One showed a benefit (although only eight cases of IE occurred),[172] and the other three found no significant protective effect.[173-175] Amoxicillin has been proven to have a significant impact on the incidence and duration of bacteremia after dental procedures.[176] However, the cost-effectiveness of amoxicillin for the prevention of IE has come into question.[177]

Despite the lack of convincing evidence for efficacy, antibiotic prophylaxis remains a class I recommendation by both AHA and ESC. Prophylaxis is primarily directed toward viridans group streptococcus and HACEK organisms before oral, respiratory, and upper gastrointestinal (GI) procedures and against *Streptococcus bovis* and enterococcus before GI and genitourinary (GU) procedures. Procedures likely to produce bacteremia and recommended antibiotic prophylaxis regimens are shown in Table 44–10.

With an age-related increase in the prevalence of valvular pathology[171,178] and the advancing age of the U.S. population, there is an increasing prevalence of cardiac valve disease that may warrant prophylaxis to prevent IE on the basis of current guidelines. This may lead to greater financial cost, development of antibiotic resistance, and adverse drug reactions, emphasizing the need for further study to determine which patients actually benefit from prophylaxis.

FUTURE DIRECTIONS

Future directions in therapy for IE include treatment with novel therapeutic agents. Bacterial adherence is central to initiation of infection and metastatic spread, and the MSCRAMM (Microbial Surface Components Recognizing Adhesive Matrix Molecules) family of bacterial surface adhesion proteins has been a target for the development of new immunotherapies. *S. aureus* Human Immune Globulin (SA-IGIV, Inhibitex, Inc.), a purified IgG derived from pooled human plasma selected for high antibody titers to the *S. aureus* MSCRAMM protein clumping factor A (ClfA), interferes with *S. aureus* adherence to extracellular matrix proteins in vitro and may also enhance opsonization and phagocytosis of *S. aureus* by PMNs.[179] In an animal model of *S. aureus* IE, combination therapy with SA-IGIV and vancomycin significantly increased clearance of bacteremia when compared with the use of vancomycin alone.[180] Aurexis is a humanized monoclonal antibody against ClfA; a phase 1 open-label trial in humans has been completed, and a phase 2 study of Aurexis in patients with MRSA IE is currently under way.[181,182]

The development and testing of vaccines to target high-risk groups may reduce adverse outcomes and the costs associated with this disease. Immunizations with fibronectin binding proteins or FimA proteins protect against experimental IE (with *S. aureus* and streptococcal species, respectively) in animal models.[183-185] StaphVax (Nabi, Inc.) is a vaccine with *S. aureus* type 5 and type 8 capsular polysaccharides, the strains accounting for more than 80% of *S. aureus* infections. In a double-blind, placebo-controlled trial StaphVax resulted in a significant 57% relative reduction in *S. aureus* bacteremia at 40 weeks in hemodialysis patients.[186] Such vaccines could have important clinical applications among patients with indwelling intravascular catheters or prostheses at high risk for *S. aureus* infections.

A shift in approach is necessary to further our understanding of IE. To develop the high-quality evidence necessary to make therapeutic decisions that improve the outcomes of our patients, we must take advantage of recent advances in technology and information systems. International collaboration in this area has led to opportunities to share data and conduct large-scale prospective cohort studies through the creation of the International Collaboration of Endocarditis (ICE) investigation. The first phase of this collaborative effort was to merge all existing databases into a single analysis database from which retrospective and descriptive studies are being performed. The second phase involved the development of a large global database of IE patients whose clinical, echocardiographic, and microbiologic findings have been characterized with standardized, predefined methods.

Since the inception of the prospective database in June 2000, 2739 patients who meet Duke criteria for definite IE have been enrolled from 59 sites in 27 countries. The multinational aspect of this study provides a global view of IE in

Table 44–10 Procedures Likely to Produce Bacteremia and Recommended Antibiotic Prophylaxis Regimens

Procedure	Antibiotic Prophylactic Regimen	Prophylactic Regimen for PCN-Allergic Patients	Notes
Dental procedures with risk of gingival/ mucosal trauma • Dental extractions • Periodontal procedures • Dental implants • Endodontic (root canal) instrumentation • Subgingival placement of antibiotic fibers or strips • Initial placement of orthodontic bands • Intraligamentary local anesthetic injections • Prophylactic cleaning of teeth **Respiratory tract and esophageal procedures** • Tonsillectomy or adenoidectomy • Surgical operations involving respiratory mucosa • Bronchoscopy with a rigid bronchoscope • Esophageal sclerotherapy or dilation	Amoxicillin 2 g PO 1 hr before procedure Unable to take PO: Ampicillin 2 g IM/IV 30 min before procedure	Clindamycin 600 mg PO 1 hr before procedure *or* Cephalexin or cefadroxil 2 g 1 hr before procedure *or* Azithromycin or clarithromycin 500 mg PO 1 hour before procedure Unable to take PO: Clindamycin 600 mg IV 30 min before procedure *or* Cefazolin 1 g IV 30 min before procedure	Avoid cephalosporins in patients with immediate-type hypersensitivity reactions to penicillins. See full reference for pediatric dosing.
Genitourinary Procedures • Lithotripsy • Cystoscopy • Prostate surgery • Urethral dilation • Gynecologic procedures in presence of infection • Biopsy urinary tract, prostate **Gastrointestinal procedures** • Surgical operations involving intestinal mucosa • ERCP with biliary obstruction • Biliary tract surgery	**High-risk patients:** ampicillin 2 g IM/IV *plus* gentamicin 1.5 mg/kg within 30 min of starting procedure *and* ampicillin 1 g IM/IV or amoxicillin 1 g PO 6 hr later **Moderate-risk patients:** Amoxicillin 2 g PO 1 hr before procedure *or* ampicillin 2 g IM/IV within 30 min of starting procedure	**High-risk patients:** Vancomycin 1 g IV over 1-2 hr plus gentamicin 1.5 mg/kg IV/IM to complete infusion within 30 min of starting procedure **Moderate-risk patients:** Vancomycin 1 g IV over 1-2 hr to complete infusion within 30 min of starting procedure	For definition of high- and moderate-risk patients, refer to Table 44–9. No second dose of vancomycin and gentamicin recommended in PCN-allergic patients Total dose of gentamicin should not exceed 120 mg. See full reference for pediatric dosing.

ERCP, endoscopic retrograde cholangiopancreatography; PCN, penicillin.
Data modified from Dajani AS, Taubert KA, Wilson W, et al: Prevention of bacterial endocarditis. Recommendations by the American Heart Association. Circulation 1997;96:358-66.

contrast to the relatively small case series largely from single centers. Identifying patients at high risk for complications and targeting this population for preventive therapy are among the potential benefits. The information gained from these efforts will be used to design and conduct randomized, controlled trials of treatment strategies that may then provide the definitive evidence necessary to assist with therapeutic decision-making.

CONCLUSION

Despite improved understanding of the pathogenesis of IE and despite the development of better diagnostic and therapeutic methods, the overall death rate for IE has changed little over the past 40 years. The use of global databases, such as ICE, can improve knowledge about this heterogeneous disease, identify populations at risk for IE and its complications, and create collaborations among investigators that will lead to new treatment and preventive strategies.

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Chapter 45

Treatment of Pericardial Disease

Brian D. Hoit

CHAPTER CONTENTS

The treatment of pericardial disease is often simple and rewarding; however, it may offer unexpected challenges and frustrations to both clinician and patient for a number of reasons. First, the presence of pericardial heart disease may elude detection, often remaining clinically silent, being apparent only during the evaluation of unrelated complaints. Moreover, although pericardial disease may present as an isolated phenomenon, it may complicate a number of systemic disorders (and indeed may be overshadowed by extracardiac manifestations). Second, although the European Society of Cardiology published guidelines for the diagnosis and management of pericardial diseases,[1] there is a paucity of randomized, placebo-controlled trials (level of evidence A) from which appropriate therapy may be selected and important clinical decisions assisted (Table 45–1). Thus the physician often must rely heavily on clinical judgment because most data originate from small, uncontrolled trials and anecdotal experience. Finally, therapeutic options in most cases are limited to nonspecific anti-inflammatory agents, drainage of pericardial fluid, and pericardiectomy. Although there is general agreement on how these measures should be applied in the patient with either mild or severe disease, there is little consensus on how the large number of cases encountered with clinical manifestations between these two extremes should be managed. Recognizing the subjective nature of many of the therapeutic recommendations, this chapter reviews the options available for treating pericardial heart disease.

ACUTE PERICARDITIS

Acute fibrinous (or "dry") pericarditis is a syndrome characterized by typical chest pain, a pathognomonic pericardial friction rub, and specific electrocardiographic changes. Hospitalization is warranted for many patients who present with an initial episode of acute pericarditis (particularly with moderate or large effusions) in order to determine an etiology and to observe for the development of cardiac tamponade; close, early follow-up is important in the remainder. Establishing the exact cause of acute pericarditis is an important part of management, but considerable judgment must be exercised when deciding whether and how to investigate the possibility of concomitant systemic disease. For example, an extensive evaluation is generally unnecessary in a young, previously healthy adult who presents with a viral syndrome, typical pericardial chest pain, and a pericardial friction rub. Despite the availability of polymerase chain reaction (PCR) and histochemistry for etiolopathogenetic classification,[2] most cases of viral pericarditis are recognized long after the period of viral activity, making a specific etiologic diagnosis and the need for antiviral chemotherapy unnecessary.

Acute pericarditis usually responds to oral nonsteroidal anti-inflammatory agents (NSAIDs), such as acetylsalicylic acid (ASA) 650 mg every 3 to 4 hours or ibuprofen 300 to 800 mg every 6 hours. Indomethacin reduces coronary blood flow and should be avoided. Prophylaxis against gastrointestinal bleeding with H2 blockers or proton pump inhibitors is warranted, particularly in those at high risk or who require longer durations of treatment. Selective COX-2 inhibitors are NSAIDs with few adverse gastrointestinal effects, but they have been implicated in adverse cardiovascular events[3]; moreover, they have not been tested in acute pericarditis. Cumulative anecdotal data suggest that colchicine (1 mg/day, with or without a 2 mg loading dose), either as a supplement to the use of NSAIDs or as monotherapy, is effective for the acute episode, is well-tolerated, and may prevent recurrences.[4] Side effects (diarrhea and nausea) are usually mild and most often do not necessitate withdrawal of the drug; long-term toxicity (azoospermia and chromosomal abnormalities) is reported in patients treated with colchicines for gout and familial Mediterranean fever.[5]

Chest pain is alleviated in 1 to 2 days, and the friction rub and ST-segment elevation resolve shortly thereafter. Most mild cases of idiopathic and viral pericarditis are adequately treated with 1 to 4 days of treatment[6]; the duration of therapy is variable, however, and patients should be treated until an effusion, if present, has resolved.[1] The intensity of therapy is dictated by the distress of the patient, and narcotics may be required for severe pain. Some cases necessitate steroid therapy (prednisone 60 to 80 mg/day) for a week to control pain, with the dosage tapered carefully on an individual basis thereafter. However, corticosteroids should be avoided unless there are specific indications (e.g., connective tissue disease, autoreactive or uremic pericarditis) because they enhance viral multiplication and may result in recurrences when the dosage is tapered; colchicine may be particularly useful in this situation. Importantly, tuberculous and pyogenic pericarditis should be excluded before steroid therapy is initiated. Intrapericardial instillation of triamcinolone (300 mg/m^2) avoids systemic side effects and is highly effective.[2] Patients in whom pericarditis

Table 45–1 Summary of the European Society of Cardiology Guidelines on the Diagnosis and Management of Pericardial Heart Disease[1]

	Indication	Evidence
Acute Pericarditis		
NSAIDs	Class I	level B
Colchicine*	Class IIa	level B
Systemic corticosteroids†	Class IIa	level B
Chronic Pericarditis		
Balloon pericardiotomy or pericardiectomy‡	Class IIb	level B
Recurrent Pericarditis		
Colchicine	Class I	level B
Systemic corticosteroids§	Class IIa	level C
Pericardiectomy¶	Class IIa	level B
Pericardial Effusion		
Pericardiocentesis for cardiac tamponade	Class I	level B
Pericardiocentesis for smaller effusions	Class IIa	level B
Analysis of Pericardial Fluid		
Pericardial fluid and blood for bacteria	Class I	level B
PCR, ADA, IFγ, lysozyme for tuberculosis	Class I	level B
PCR, in situ hybridization for virus	Class IIa	level B
Serum viral titers	Class IIb	level B
Pericardial chemistry (specific gravity, protein, LDH, glucose)	Class IIb	level B
Specific Forms of Pericarditis		
Corticosteroids for TB pericarditis	Class IIb	level A
Pericardiocentesis for tamponade and large effusions unresponsive to dialysis	Class IIa	level B
Pericardiocentesis for large neoplastic effusions	Class I	level B
Diagnostic pericardiocentesis in suspected neoplastic effusion	Class IIa	level B
Intrapericardial instillation of cytotoxic/sclerosing agent for neoplastic pericarditis	Class IIa	level B
Radiation Rx for control of effusions in patients with radiosensitive tumors	Class IIa	level B
Percutaneous balloon pericardiotomy for malignant effusions	Class IIa	level B
Pleuropericardiotomy to drain malignant effusions	Class IIb	level C
Surgical therapy of chylous effusion resistant to diet and pericardiocentesis	Class I	level B
Thyroid hormone for effusion secondary to myxedema	Class I	level B

*For initial attack and prevention of recurrences.
†For connective tissue disease–associated, autoreactive, and uremic effusions.
‡For frequent and symptomatic recurrences.
§For recurrent pericarditis in patients in poor general condition or in frequent crises.
¶For frequent, highly symptomatic recurrences resistant to medical therapy.
ADA, adenosine deaminase; IFγ, interferon gamma; LDH, lactate dehydrogenase; PCR, polymerase chain reaction.

represents one manifestation of systemic illness (e.g., sepsis, uremia, connective tissue disease, neoplasia) should, in addition to palliative and supportive treatment, also receive therapy directed toward the primary disorder.

RECURRENT PERICARDITIS

Recurrent or relapsing acute pericarditis is one of the most distressing disorders of the pericardium for both patient and physician. It may occur with or without pericardial effusion and occasionally is associated with pleural effusion or parenchymal pulmonary lesions. Atypical features, such as the absence of physical findings, offer challenges for diagnosis and management and often necessitate close follow-up and rigorous emotional support. Recurrences occur with highly variable frequency over a course of many years; although they may be spontaneous, occurring at varying intervals after discontinuation of drug (i.e., "recurrent"), they are more commonly associated with either discontinuation or tapering of anti-inflammatory drugs (i.e., "incessant").

Painful recurrences of pericarditis may respond to NSAIDs but commonly require corticosteroids. Once steroids are administered, dependency and the development of steroid-induced abnormalities are potential perils. Prednisone is begun at a high dose (1 to 1.5 mg/kg/day) for at least 4 weeks and tapered slowly over the next 3 months.[7] Tapering to the lowest possible dose, using alternate day therapy, or combinations with NSAIDs should minimize the risks associated with long-term steroids. In the most difficult cases, relapse occurs each time the dose of prednisone is reduced to less than 5 to 20 mg/day. When this occurs, the patient should be maintained for several weeks on the lowest suppressive dose before the next taper commences. A recent multicenter trial of 51 patients followed for up to 10 years suggests that colchicine is both efficacious and safe for the prevention of recurrences.[8]

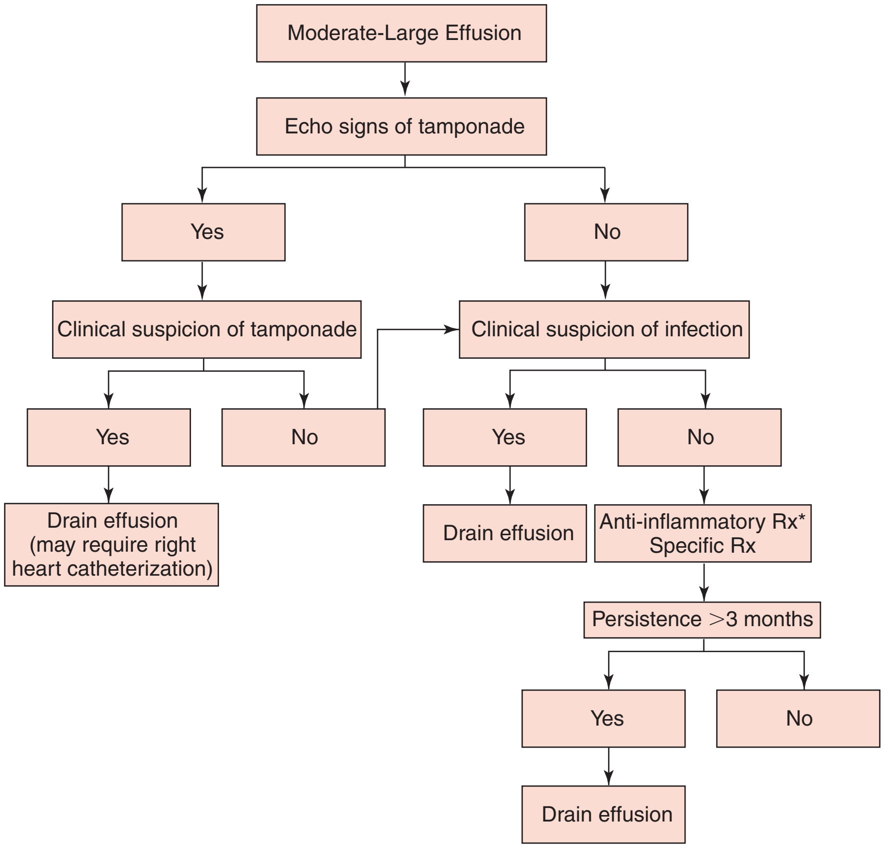

Figure 45–1 Algorithm for the management of moderate to large pericardial effusions. *Anti-inflammatory treatment if there are signs of pericarditis. (Redrawn with permission from Hoit BD: Management of effusive and constrictive pericardial heart disease. Circulation 2002;105:2939-42.)

Most authors recommend 1 mg/day p.o. for at least 1 year with a gradual taper; the need for a loading dose of 2 to 3 p.o. mg is unsettled. Azathioprine and cyclophosphamide have been used to prevent recurrent episodes in patients who fail to respond to high-dose corticosteroids or who experience severe corticosteroid side effects.[7] Although encouraging results have been reported in a series of patients who underwent surgery for recurrent pericarditis, pericardiectomy may simply abbreviate, rather than terminate, the painful recurrences. Therefore, pericardiectomy should be considered only when repeated attempts at medical treatment have clearly failed, especially when there is evidence (or at least well-grounded suspicion) of steroid-induced complications.

PERICARDIAL EFFUSION AND TAMPONADE

In the absence of tamponade or suspected purulent pericarditis, there are few indications for pericardial drainage. Persistent large and unexplained effusions (especially when tuberculosis is suspected or present for more than 3 months) may warrant pericardiocentesis. Occasionally, suspected malignancy or systemic disease may necessitate pericardial drainage and biopsy. However, *routine* drainage of large effusions (20-mm, echo-free space in diastole) has a low diagnostic yield (7%) and no therapeutic benefit.[9] Figure 45–1 presents an approach to the management of moderate and large pericardial effusions.

Remembering that clinically significant tamponade is a clinical diagnosis and "echocardiographic signs of tamponade" are not by themselves an indication for pericardiocentesis is important. Although the absence of any cardiac chamber collapse has a high negative predictive value (92%), the positive predictive value is reduced (58%); and although positive and negative predictive values were high (82% and 88%, respectively) for abnormal right-sided venous flows (i.e., systolic predominance and expiratory diastolic reversal), they could not be evaluated in more than one third of patients.[10]

Removal of small amounts of tamponading pericardial fluid (≈50 mL) produces considerable symptomatic and hemodynamic improvement because of the steep pericardial pressure-volume relation. Unless there is concomitant cardiac disease or coexisting constriction (i.e., effusive-constrictive pericarditis), removal of all of the pericardial fluid normalizes pericardial, atrial, ventricular diastolic and arterial pressures, and cardiac output (see Fig. 45–1). Mild or low pressure tamponade (i.e., when the venous pressure is < 10 cm of water, arterial blood pressure is normal, and pulsus paradoxus is absent), particularly when the etiology is idiopathic, viral, or when responsive to specific therapy (e.g., thyroid hormone), does not require pericardiocentesis. At the other extreme, hyperacute tamponade (usually resulting from cardiac trauma) necessitates immediate pericardiocentesis as an initial triage measure. However, most patients fall between these two extremes and will require pericardial drainage. Either surgical means (via subxiphoid incision, video-assisted thoracoscopy, or thoracotomy) or percutaneous means (with a needle or balloon catheter) accomplishes pericardial drainage.

Unless the situation is immediately life threatening, experienced staff should perform pericardiocentesis in a facility equipped with radiographic, echocardiographic, and hemodynamic monitoring to optimize the success and safety

Table 45–2 Advantages and Disadvantages of Pericardial Drainage Methods

Method	Advantages	Disadvantages
Pericardiocentesis	Acquisition of hemodynamic data Provides effective relief, particularly if no clots Less postoperative pain than other methods	No biopsy material available Effusion may recur Drainage may not be adequate, particularly if effusion is loculated
Pericardiotomy (subxiphoid or balloon)	Clots and loculations removed "Minor" surgical procedure	Evacuation may not be complete Frequent pericardial-pleural window closure
Open Surgical Drainage	Complete drainage Less reaccumulation, constriction (if total pericardiectomy) Access to pericardial tissue Avoidance of "blind" trauma to pericardium	Surgical procedure Hemodynamics not readily available Longer hospitalization, more postoperative pain

of the procedure. Monitoring the cardiac rhythm and systemic blood pressure is a minimum requirement. Invasive hemodynamics and measurement of pericardial pressures are useful for the diagnosis, particularly in questionable cases. Monitoring the local electrocardiogram from the needle tip is not recommended by all authors, and if such monitoring is employed, it is essential that the apparatus have equipotential grounding. The advantages of needle pericardiocentesis include the ability to perform careful hemodynamic measurements and relatively simple logistic and personnel requirements (Table 45–2). The safety of the procedure has been increased by using 2-D echo guidance (Fig. 45–2).[11]

The patient's back should be elevated at an approximately 30-degree angle to assist anterior and inferior pooling of the effusion. The subxiphoid approach is preferred because of its extrapleural and relatively avascular location. Echocardiographic or computed tomographic guidance assists pericardial drainage using alternative sites on the chest wall. Except in the most desperate measures, a short beveled needle, 5 to 8 cm long (unless the patient is morbidly obese) should be used. The needle track is anesthetized with 1% lidocaine, and the skin is pierced with a blade approximately 5 mm below and to the left of the subxiphoid process. The needle is attached via a three-way stopcock to a pressure transducer and an aspiration syringe containing 1% lidocaine and is advanced at an approximately 90-degree angle to the skin until the inner aspect of the rib cage is reached. The hub of the needle is then depressed and angled toward the left shoulder, and the needle is advanced cautiously with a 15-degree posterior tilt using a "worm gear" turning action. Deeper tissues are anesthetized with small injections of lidocaine that follow attempts to aspirate fluid. Upon puncturing the parietal pericardium, a slight "give" may be appreciated. Unsuccessful aspiration (or epicardial contact, which may be indicated by a current of injury, ventricular ectopic beats, or transmission of a "tickling" sensation in the fingers) calls for posterior reorientation of the hub or the redirection of the needle toward the right shoulder.[6] Injection of agitated saline or small quantities of radiographic contrast and imaging can make confirmation of pericardial puncture with echocardiography or fluoroscopy, respectively (Fig. 45–3). Unless there has been massive intrapericardial hemorrhage, bloody fluid originating from the pericardium does not clot.

A 6- to 8-cm French catheter may be placed over a guidewire when pericardial fluid can be freely withdrawn, and the catheter left in place for continued drainage (using only slight negative pressure). Drainage of the pericardial fluid using a catheter minimizes trauma, allows measurement of pericardial pressure and instillation of drugs into the pericardium, and helps prevent (but does not guarantee) reaccumulation of pericardial fluid. Extended (3 ± 2 days) catheter drainage is associated with a trend toward lower recurrence rates over a nearly 4-year follow-up.[12] Generally speaking, drainage should continue until the volume of the aspirated volume is less than 25 mL/day. The site of skin puncture should be covered with antiseptic ointment and a sterile dressing during catheter drainage.

Although pericardiocentesis is usually well tolerated, pulmonary edema, circulatory collapse, and acute right and left ventricular dysfunction have been reported after drainage.[13-15] Patients should be monitored for recurrent tamponade, particularly those with hemorrhagic effusions, which may occur despite the presence of an intrapericardial catheter. Dilute heparin or fibrinolytic agents may be instilled in the catheter to prevent clotting. Patients generally should be observed for 24 hours in an intensive care unit.

Major complications of pericardiocentesis include laceration of a coronary vessel, perforation of the myocardium (the thin-walled coronary veins and right heart chambers are particularly prone to brisk bleeding), hypotension (often reflex in origin), arrhythmia (both atrial and ventricular), perforation of a lung, or gastrointestinal viscus.

Although pericardiocentesis may provide effective relief, percutaneous balloon pericardiotomy, subxiphoid pericardiotomy, or the surgical creation of a pleuropericardial or a peritoneal-pericardial window[16,17] may be required. In a retrospective review, pericardiocentesis with intrapericardial sclerotherapy was as effective as an open surgical drainage procedure in patients with malignant pericardial effusion.[18] However, the safety and efficacy of subxiphoid pericardiostomy was found to be superior to percutaneous drainage in both benign and malignant effusions. The authors of the latter study recommended that percutaneous needle drainage be reserved for patients with hemodynamic instability.[16]

Open surgical procedures offer several advantages including complete drainage, access to pericardial tissue for histopathologic and microbiologic diagnoses, the ability to evacuate loculated effusions, and the absence of traumatic injury owing to the blind placement of a needle into the pericardial space. The choice between needle pericardiocentesis

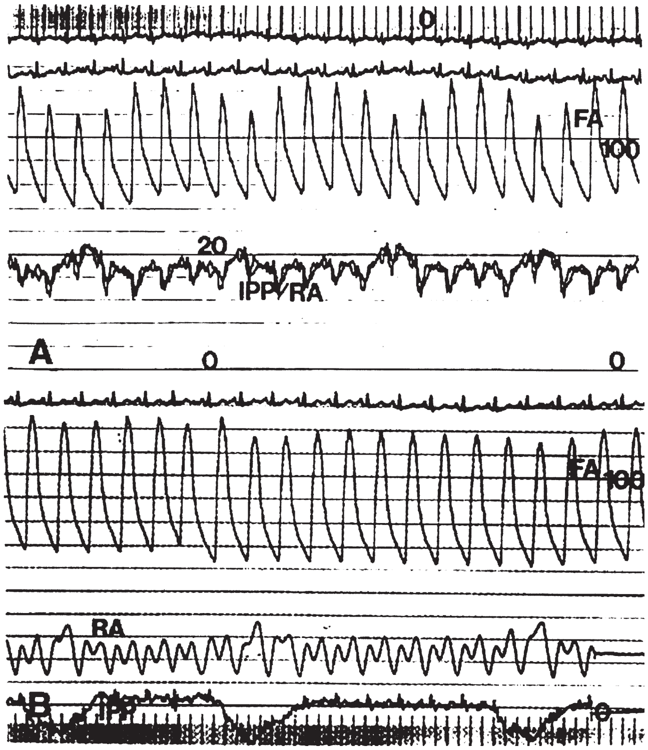

Figure 45–2 Hemodynamic record from a patient with cardiac tamponade before *(A)* and after *(B)* pericardiocentesis. **A**. Pulsus paradoxus is evident from the femoral artery *(FA)* pressure tracing. Note the absent Y descent on the right atrial *(RA)* tracing and the equal and elevated RA and pericardial *(IPP)* pressures. **B**. After removal of pericardial fluid, pericardial and right atrial pressures decrease and the pulsus paradoxus disappears. (Courtesy Noble O. Fowler, MD. From Hoit BD: Pericardial disease and pericardial heart disease. In O'Rourke RA (ed): Steins's Internal Medicine, 5th ed. St. Louis, Mosby–Year Book, 1998, p 273.)

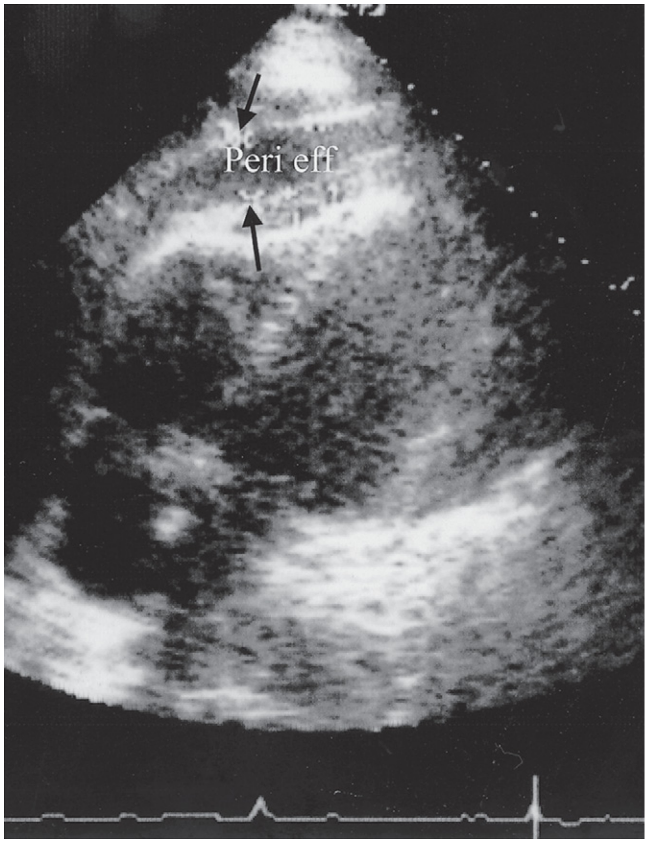

Figure 45–3 Two-dimensional echocardiographic image of an acute pericardial effusion (Peri eff) complicating percutaneous transluminal myocardial revascularization. Localization of a loculated collection of fluid is used to direct needle pericardiocentesis.

and surgical drainage depends on institutional resources and physician experience, the etiology of the effusion, the need for diagnostic tissue samples, and the prognosis of the patient. Needle pericardiocentesis is often the best option when the etiology is known or the diagnosis of tamponade is in question, or both, and surgical drainage is optimal when the presence of tamponade is certain but the etiology is unclear. Pericardiocentesis is ill-advised when there is less than 1 cm of effusion, loculation, or evidence of fibrin and adhesion (Fig. 45–4). It should be recognized that surgical approaches (subxiphoid pericardiotomy or thoracoscopic drainage) can be performed using local anesthesia with little attendant morbidity. Irrespective of the method of retrieval, pericardial fluid should be sent for hematocrit and cell count; glucose; Gram, Ziehl-Nielsen, and fungal smears; viral, bacterial, and fungal culture; and cytology. Depending on the clinical circumstances, cytology; tumor markers and carbohydrate antigens (for suspected malignant disease); and adenosine deaminase, interferon gamma, pericardial lysozyme, and PCR analysis (for suspected tuberculosis) should be obtained.

IV saline solution should be given to patients with cardiac tamponade awaiting pericardial drainage in an effort to expand the intravascular volume. However, volume expansion may only be of value in hypovolemic patients.[19] Dobutamine or nitroprusside may be used to increase cardiac output after the blood volume has been expanded, but only as a temporizing measure. Vagal reflexes complicating tamponade or pericardiocentesis are treated with atropine (1 mg IV). Positive pressure breathing should be avoided because it reduces venous return, right ventricular transmural pressure, and cardiac output.

Recurrent effusions may be treated by either repeat pericardiocentesis, sclerotherapy with tetracycline, surgical creation of a pericardial window, or pericardiectomy. Subtotal pericardiectomy is preferred when the patient is expected to survive more than 1 year. A pleuropericardial window provides a large area for fluid to be reabsorbed and is often performed in patients with malignant effusions. Pericardiectomy may be required for recurrent effusions in dialysis patients. In critically ill patients, a pericardial window may be created percutaneously with a balloon catheter.[20,21]

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis is a condition in which a thickened, scarred, and often calcified pericardium limits diastolic filling of the ventricles. Although acute pericarditis from most causes may eventuate in constrictive pericarditis, the most common

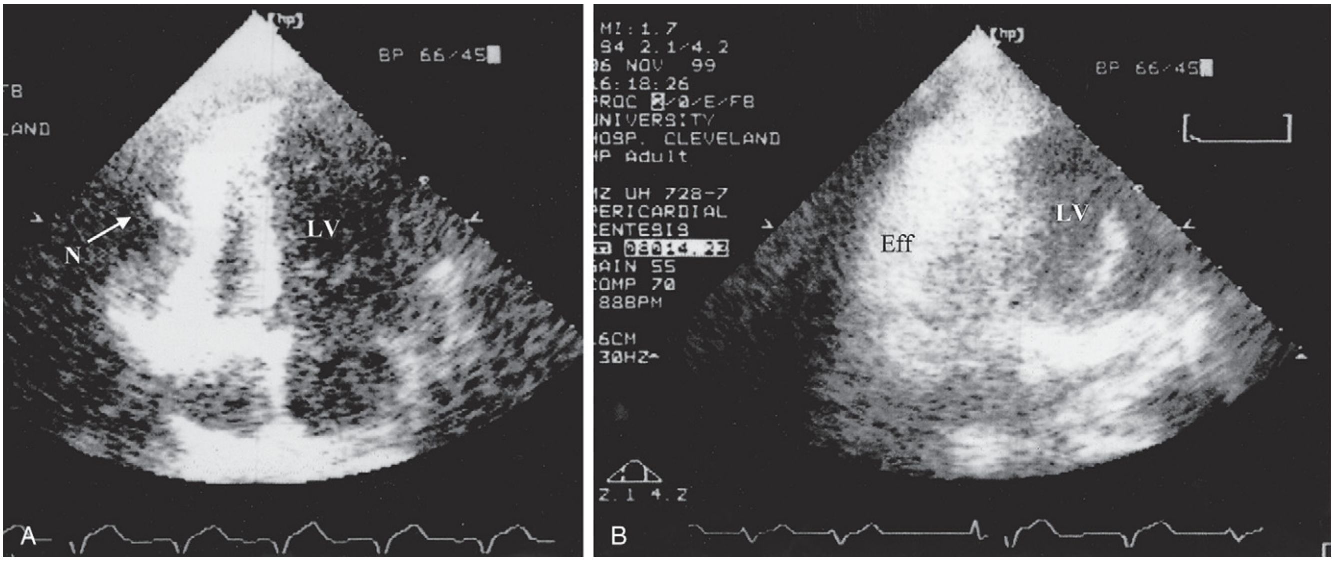

Figure 45–4 Echocardiographic imaging can be used to verify the intrapericardial location of the needle *(N)* by either direct imaging **(A),** or by the production of an intrapericardial contrast effect *(Eff)* after injection of agitated saline **(B).** LV, left ventricle.

antecedents are idiopathic pericarditis, cardiac trauma and surgery, mediastinal irradiation, tuberculosis (particularly common in nonindustrialized countries) and other infectious diseases, neoplasms (particularly lung and breast), renal failure, and connective tissue diseases. Although it is commonly thought that a normal pericardial thickness excludes the diagnosis of constrictive pericarditis, 28% of 143 surgically confirmed cases had normal pericardial thickness on CT scan and 18% had normal thickness on histopathologic examination.[22]

Classic *chronic constrictive pericarditis* is less frequently encountered than in the past, whereas *subacute constrictive pericarditis* (weeks to months after the inciting injury, such as after cardiac surgery) is becoming more common. In this latter group of patients, constriction may be transitory, with a course that may span a matter of weeks to a few months. Not surprisingly, pericardial calcification is uncommon. Doppler-detected constrictive physiology resolved without pericardiectomy in 36 of 212 patients studied retrospectively at Mayo Clinic after an average of approximately 8 weeks.[23] In asymptomatic patients *(occult constrictive pericarditis)*, exercise testing and, if available, maximal O_2 consumption should be quantified, jugular venous pressure carefully estimated, and liver function tests measured. Increasing jugular venous pressure, the need for diuretic therapy, evidence of hepatic insufficiency, and reduced exercise tolerance indicate the need for surgery.

Pericardiectomy is the definitive treatment for constrictive pericarditis but is unwarranted either in early constriction (occult and functional class I) or in severe, advanced disease (functional class IV), when the risk of surgery is excessive (operative mortality 30% to 40% versus 6% to 19%) and the benefits are diminished.[24,25] Because some cases of constriction resolve spontaneously, it is prudent that patients with subacute constrictive pericarditis who are hemodynamically stable be given a trial of conservative management for 2 to 3 months until it is clear that the constrictive process is permanent before pericardiectomy is recommended. After pericardiectomy, symptomatic relief and normalization of cardiac pressures may take several months, occurring sooner when the operation is carried out before the disease becomes too chronic (calcification may correlate with disease chronicity in populations with a low incidence of tuberculous pericarditis[26]) and when the pericardiectomy is almost complete. Complete or extensive pericardial resection is desirable. In one study, the long-term outcome was predicted by three variables in a stepwise logistic regression analysis. Specifically, the prognosis was worse with increasing age and New York Heart Association class and a postirradiation etiology.[25] In another study, age, renal dysfunction, pulmonary hypertension, left ventricular dysfunction, and hyponatremia were independent adverse predictors.[27]

Pericardiectomy is commonly carried out via a median sternotomy, although some surgeons prefer access through a thoracotomy. Despite a decline, the risk of mortality remains approximately 6% to 19%. The risk is increased by heavy calcification and involvement of the visceral pericardium. Left ventricular systolic dysfunction may occur after decortication of a severely constricted heart. Although the left ventricular dysfunction may require treatment for several months, it usually resolves completely. In highly selected patients, orthotopic transplantation may be considered.[25]

Medical therapy of constrictive pericarditis has a small but important role. In some patients constrictive pericarditis resolves either spontaneously or in response to various combinations of nonsteroidal anti-inflammatory agents, steroids, and antibiotics[23]; in the remaining patients medical therapy is adjunctive. Specific antibiotic (e.g., antituberculous) therapy should be initiated before surgery and continued afterward. Preoperative diuretics should be used sparingly with the goal of reducing, not eliminating, elevated jugular pressure, edema, and ascites. Postoperatively, diuretics should be given if spontaneous diuresis does not occur. The central venous pressure may take weeks to months to return to normal after pericardiectomy. The left ventricular ejection fraction may decrease postoperatively, only to return to normal months later. In the interim, digoxin, diuretics, and vasodilators may

be useful. Diuretics and digoxin (in the presence of atrial fibrillation) are useful in patients who are not candidates for pericardiectomy because of their high surgical risk.

Prevention of pericardial constriction consists of appropriate therapy of acute pericarditis and adequate pericardial drainage. Although instillation of fibrinolytics (urokinase 400,000 U per instillation to 1,600,000 U; streptokinase 250,000 IU per instillation to 1,000,000 IU) is promising, corticosteroid instillation is often ineffective.[28-29]

TREATMENT OF SPECIFIC CAUSES OF PERICARDITIS

Purulent Pericarditis

The incidence and bacterial spectrum of purulent pericarditis have changed because of the increasing frequency of cardiac surgery and instrumentation, selection-induced changes in the flora responsible for hospital-acquired infections, and the prolonged survival of immunocompromised hosts. Bacterial pericarditis is treated with surgical exploration and drainage (pericardiectomy is preferable) and appropriate systemic antibiotics, which should be considered adjuvant. A high index of suspicion is critical because in the appropriate setting, pericardial involvement is often unrecognized when it complicates systemic infection, and the characteristic features of acute pericarditis are frequently absent. The threshold for echocardiography in the septic patient should be low, and whenever purulent pericarditis is suspected, the pericardial space should be explored. Iodine-containing irrigants may provoke constriction and should be avoided. Fibrinolytics (see earlier) may be used to lyse fibrous adhesions, liquefy purulent exudate, and prevent constrictive pericarditis.[28-29]

Mycobacterial and Fungal Pericarditis

Tuberculosis is a major cause of pericarditis in nonindustrialized countries but is an uncommon cause of pericarditis in the United States. Nevertheless, its incidence is increasing because of HIV infection.[30] Tuberculous pericarditis results from hematogenous spread of primary tuberculosis or from breakdown of infected mediastinal lymph nodes, and therefore typical symptoms and signs and radiologic evidence of pulmonary tuberculosis are usually absent. Fibrinous pericarditis with caseating necrosis and mononuclear infiltrate gives rise to an effusive phase, which is often voluminous and hemodynamically significant. An adhesive phase follows resolution of the effusion and eventuates in dense, calcific adhesions with clinical constriction in nearly one half of patients.

The diagnosis of tuberculous pericarditis is based on (1) histologic identification, (2) culture of *Mycobacterium tuberculosis*, (3) pericarditis with proven extracardiac tuberculosis, or (4) pericardial effusion responsive to antituberculosis therapy. PCR-detected *M. tuberculosis* DNA, high adenosine deaminase activity, and interferon gamma concentration in the pericardial fluid are also diagnostic.[1] Fluid should be removed and cultured, and antituberculous therapy should begin. Depending on the echocardiographic appearance, subxiphoid drainage may be necessary. Early pericardiectomy has been recommended by some in all cases of tuberculosis pericarditis, but the long-term (16 years) prognosis of patients without cardiac compression during the acute illness who are treated with medical therapy alone is excellent.[31] Multiple drug therapy and corticosteroids are effective in tuberculous pericarditis, whereas atypical mycobacterial infections (especially *M. avium-intracellulare*) may be resistant to treatment. Patients with tuberculous pericarditis should receive triple drug therapy (isoniazid 5 mg/kg to a maximum of 300 mg, rifampin 10 mg/kg to a maximum of 600 mg, and either streptomycin 15 mg/kg to a maximum of 1 g or ethambutol 5 to 25 mg/kg to a maximum of 2.5 g) for a minimum of 9 months. Corticosteroids (prednisone 1 to 2 mg/kg/day) may be useful if pericardial effusion persists or recurs during therapy and are beneficial acutely in reducing morbidity and mortality, but definitive data supporting their use to prevent constriction in primary pericardial effusion are lacking.[32] Pericardiectomy may be necessary for recurrent cardiac tamponade.

Patients should be observed for constriction because up to half of them will require pericardiectomy.[33] Failure to improve or worsening over 1 to 2 months, pericardial thickening, or evidence of constriction require urgent pericardiectomy.[6] For patients with hemodynamics consistent with effusive-constrictive pericarditis, plans for visceral and parietal pericardiectomy after a few weeks of chemotherapy should be made. Persistent hypotension may signify tuberculous adrenal insufficiency.

Pericarditis complicating deep fungal infection with *Histoplasma* or *Coccidioides* immitis may be immunologic, resolve spontaneously, and not require specific therapy. Amphotericin B (up to 2.5 g total), itraconazole (200 to 400 mg/day), ketoconazole (200 to 400 mg/day), and fluconazole (200 to 400 mg/day) are rarely required. Tamponading effusion and constriction require decompression.

Surgical decompression and specific antifungal or antimicrobial therapy may be necessary for disseminated infection with *Candida, Aspergillus, Actinomycetes,* and *Nocardia.*

HIV-Associated Pericarditis

Human immunodeficiency virus (HIV) is an important cause of pericardial heart disease. Typically, pericardial effusions are small and asymptomatic in outpatients, but large effusions and tamponade are common in hospitalized patients with late-stage AIDS. Large, symptomatic pericardial effusion in patients with HIV infection should be aggressively investigated, as two thirds of these cases have an identifiable cause.[34] Tamponade in patients with HIV is mycobacterial (*M. tuberculosis* or *avium-intracellulare*) in origin in approximately one third of patients.[34]

Neoplastic Pericarditis

Metastatic neoplasia remains the leading cause of pericardial disease in hospitalized patients, most often in patients with lung or breast cancer, melanoma, lymphoma, and acute leukemia. Many cases are asymptomatic and are found only incidentally at autopsy, but others cause symptoms and may progress to cardiac tamponade. The pericardium may be thickened and cause constriction; less commonly, effusive-constrictive pericarditis occurs.

In almost all cases, fluid should be removed if large effusions are refractory or if tamponade ensues.[35] The specific

approach depends on the patient's expected longevity and medical condition. Pericardiocentesis is associated with a high recurrence rate and does not provide tissue for biopsy. Sclerosing agents, such as tetracycline (500 to 1000 mg in 20 mL of sterile saline), reduce recurrences and their use can be considered for patients with a poor prognosis. However, sclerosis is painful, does not improve prognosis, and may not be superior to an indwelling catheter alone. Subtotal pericardiectomy is most effective but should only be performed in carefully selected patients. Balloon pericardiotomy avoids the discomfort and risk of surgery and will likely replace surgical subxiphoid pericardiotomy in critically ill patients with predictably limited survival.[36] Radiation therapy and intrapericardial instillation of P32-colloid (a colloidal suspension of radioactive phosphorus) are effective strategies to control pericardial effusion but are not without significant practical difficulties and toxicities.[35,37]

Pericarditis Complicating Myocardial Infarction

Pericarditis is common in the first few days after myocardial infarction, occurring in up to 28% to 43% of fatal infarctions, but is clinically apparent in 7% of cases[38] (see Chapter 47 of *Heart Disease,* 7th edition). Pericardial involvement is related to infarct size and is associated with a poor prognosis.[39] An important clinical issue is the extent to which acute pericarditis in myocardial infarction influences management with anticoagulants. A pericardial friction rub that occurs in the first 2 or 3 days without an associated pericardial effusion should not influence clinical decisions, but pericarditis that occurs later in the course or is accompanied by pericardial effusion or tamponade is a contraindication to anticoagulant therapy. Cardiac tamponade seldom occurs, except in patients who receive systemic anticoagulants or who have cardiac rupture.

Treatment of infarct pericarditis is seldom indicated, but when symptomatic, infarct pericarditis responds to ASA (up to 650 mg every 4 hours by mouth for 5 to 10 days); corticosteroids should be avoided because of concerns with impaired infarct healing, steroid dependency, and toxic side effects.

Reperfusion therapy almost invariably precedes the development of pericarditis; therefore clinical decision making is not usually affected. Reperfusion therapy reduces the incidence of postinfarction pericarditis by approximately one half,[40] and for reasons not entirely clear, has helped render late postmyocardial infarction pericarditis nearly obsolete.[41] When it occurs, Dressler's syndrome is treated similarly to idiopathic acute effusive pericarditis.

Radiation-Induced Pericardial Disease

Acute pericarditis that occurs early during radiation therapy is uncommon and is most likely the result of radiation-induced effects on the tumor rather than a direct toxic effect of radiation on the pericardium.[42] In this instance, therapy should not be disrupted, although a reduction in dose may be necessary. A delayed (usually less than 1 year, but highly variable) form of pericardial injury may present as acute pericarditis or effusion (often with some degree of cardiac compression). The reaction of the pericardium to radiation is fibrinous inflammation,[43] often with an effusion. Although the acute lesion usually subsides within 2 years without sequelae, constrictive and effusive-constrictive pericarditis may manifest only after many years.

In the effusive stage the differential diagnosis includes recurrence of the neoplasm; examination of pericardial fluid is then helpful because the fluid frequently shows evidence of malignancy.[44,45] When the diagnosis remains in doubt, biopsy, particularly epicardial biopsy, may be necessary.[46] Effusion may be due to a radiation therapy–induced hypothyroid state.

Acute radiation-induced pericarditis can be managed symptomatically as acute idiopathic pericarditis. Hemodynamically insignificant pericardial effusion can also be managed conservatively, as spontaneous resolution is the rule; however, pericardiectomy should be offered to symptomatic patients with large, recurrent pericardial effusions. Constrictive pericarditis requires pericardiectomy unless a biopsy (obtained to distinguish constriction versus restrictive cardiomyopathy secondary to radiation) reveals significant endomyocardial fibrosis.

Traumatic Pericardial Disease

Blunt and penetrating trauma are important causes of pericarditis, particularly among young males. Chronic constrictive pericarditis, recurrent pericardial effusion, and recurrent acute pericarditis are well-recognized complications of such trauma. Although traumatic pericarditis is often overshadowed by associated injuries and usually resolves uneventfully, pericardial involvement may be life threatening. Echocardiography used in the trauma unit rapidly and accurately diagnoses hemopericardium in patients with potentially penetrating cardiac wounds.[47] Failure to repair the injury responsible for tamponade is associated with a poor clinical outcome.[48] Constrictive pericarditis occasionally occurs and may be delayed, presenting for weeks or years after the injury.[49]

Chylopericardium

Chylous pericardial effusions generally follow traumatic or surgical injury to the thoracic duct but may result from neoplastic obstruction of the thoracic duct (secondary chylopericardium); less commonly, they may be idiopathic (primary). Failure to respond to a diet rich in medium chain triglycerides and pericardiocentesis warrants ligation of the thoracic duct and pericardiectomy.[50] In cases deemed inappropriate for aggressive therapy, a valved pericardioperitoneal conduit can be implanted.[51]

Pericardial Disease in Patients with Renal Failure

Pericarditis complicates both uremia and dialytic therapy (hemoperitoneal and peritoneal) and may be clinically silent. The clinical manifestation of nephrogenic pericardial disease may be acute fibrinous pericarditis, pericardial effusion, or cardiac tamponade; classic constrictive pericarditis is rare.

Although intensification of dialysis is an accepted treatment modality for hemodynamically insignificant disease, considerable controversy exists regarding the optimal management of large, persistent, or recurrent pericardial effusion. Tamponade is an indication for pericardial drainage, and

large, resistant chronic effusion warrants pericardiocentesis. A conservative approach, such as intensification of dialysis and NSAIDs, may suffice in less severe cases. The instillation of nonabsorbable steroids (triamcinolone 50 mg every 6 hours for 2 to 3 days) directly into the pericardial space has been advocated,[52] but randomized controlled data about this form of therapy are absent. If needle drainage is necessary, an indwelling catheter should be left in the pericardial space for at least 2 to 3 days. Dialysis-associated effusive pericarditis usually responds to an intensification of dialysis and regional heparinization or by changing to peritoneal dialysis. Pericardiectomy may be necessary for intractable effusions.

Myxedema Pericardial Disease

Pericarditis with effusion (sometimes containing cholesterol) occurs in about one third of patients with myxedema. Effusions develop slowly and may reach prodigious size; slow resolution usually follows institution of thyroid replacement therapy. Pericardial drainage is generally not indicated because myxedema effusions seldom cause tamponade.

Connective Tissue Disease–Related Pericardial Disease

Pericarditis may accompany virtually any connective tissue disease and present as either acute or chronic pericarditis with or without an effusion.[53] Although tamponade, effusive-constrictive disease, and constrictive pericarditis are recognized complications, most cases are subclinical and in many instances are recognized only at autopsy. In the absence of tamponade or secondarily infected effusions, NSAIDs and corticosteroids are useful.

Pericardial Disease and Pregnancy

Small- to moderate-sized effusions occur in the last trimester of approximately 40% of healthy pregnancies, whereas larger accumulations should raise concern of another disorder.[54] Most pericardial diseases in pregnancy are managed as for the nonpregnant patient. However, colchicine is contraindicated and high-dose ASA may prematurely close the ductus.[54] Pericardiocentesis should be reserved for large, tamponading effusions and suspected infection; echocardiographic guidance avoids fetal irradiation.

Drug-Induced and Iatrogenic Pericardial Disease

A wide variety of drugs and toxins may cause pericardial heart disease (Table 45–3), by producing either drug-induced lupus, a hypersensitivity or idiosyncratic reaction, pericardial irritation, or hemorrhage. Cardiac tamponade after thrombolysis with tPA given for stroke was recently reported.[55]

Iatrogenic pericardial disease results from both the calculated complications and the unanticipated misadventures of diagnostic and therapeutic procedures. Specific management depends on the particular procedure; for example, although

Table 45–3 Drugs and Toxins Implicated as Causing Pericardial Heart Disease

Drug-induced Lupus	Hypersensitivity or Idiosyncratic Reaction	Pericardial Irritation/Hemorrhage
Procainamide	Penicillins, sulfas	Anticoagulants
Tocainide	Cephalosporins	Thrombolytics
Hydralazine	Streptomycin	Pericardial contact with:
Methyldopa	Ara-C	Tetracycline
Phenytoin	Minoxidil	Talc
Reserpine	Practolol	Asbestos
Mesalazine	Thiazides	Silicones
Isoniazid	Amiodarone	
Betaxolol	Cyclophosphamide, azathioprine	
	Anthracyclines	
	Psicofuranine	
	5-Fluorouracil	
	Methotrexate	
	Cyclosporine	
	Methysergide, ergoline drugs	
	Cromolyn sodium	
	Carbamazepine	
	Clozapine	
	Streptokinase	
	Phenylbutazone	
	Doxorubicin	
	Polymer fume inhalation	
	Vaccines (smallpox, yellow fever)	
	GM-CSF*, cytokines (IL2, IFα)	
	Serum sickness, scorpion fish sting	

*Granulocyte-macrophage colony-stimulating factor.
Modified from Spodick DH: The Pericardium. A Comprehensive Textbook. New York, Marcel Dekker, 1997.

transeptal punctures may require rescue pericardiocentesis, perforation of a coronary artery by a guidewire may require only withdrawal of the wire and watchful waiting. Coronary artery transections during coronary interventional procedures are treated with either a covered stent or perfusion balloon. Routine echocardiography is recommended after myocardial biopsy and pacemaker lead implantation.[1]

Anticoagulation in Pericarditis

The management of anticoagulation in patients with acute pericarditis and effusion requires analysis of the competing risks and benefits; few objective data are available for decision-making. In a study of seven patients with recent anterior wall myocardial infarction and pericarditis (small effusion in five, moderate in two), apical LV thrombi were successfully treated with parenteral heparin and long-term oral anticoagulation.[56] Acute pericarditis generally responds to NSAIDs within a few days, during which time anticoagulants may be withheld in low-risk patients; patients at higher thromboembolic risk can be switched to heparin while awaiting a clinical response. Unexplained effusions should be thoroughly evaluated to exclude hemorrhage.

Acknowledgment

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Optimal Timing of Surgical and Mechanical Intervention in Native Valvular Heart Disease

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CHAPTER CONTENTS

INTRODUCTION

The timing of surgical intervention in the management of isolated native valvular dysfunction depends on several elements. The presence of symptoms is important and often reflects the hemodynamic burden that lesions place on ventricular size and function. When lesions are mild in severity, ventricular systolic function remains largely unchanged and the patient remains asymptomatic. However, as lesions progress in severity, their hemodynamic impact may begin to emerge as ventricular geometry and function change. Cardiovascular symptoms may eventually follow, and if then left untreated, persistent ventricular dysfunction and circulatory compromise may ensue. It is therefore a triad of lesion severity, ventricular function, and symptomatology that largely guides the timing of intervention in an effort to avoid irreversible ventricular dysfunction and cardiovascular morbidity and mortality.[1]

Advances in technology have enabled the accurate noninvasive detection and assessment of valvular dysfunction. In particular, echocardiography has become the cornerstone of assessment of valvular lesions. The hemodynamic impact of valvular heart disease can be readily assessed and quantified using multiparametric analyses that include an assessment of ventricular size and function.[2] In some cases, however, the severity of valvular disease may be ambiguous or disparate from other clinical findings, leaving the diagnosis of severity in doubt. In these cases, invasive hemodynamics can be obtained at cardiac catheterization and used to help clarify lesion severity. Still, the severity of the lesion alone does not necessarily mandate surgical correction.

Corrective therapy for valvular heart disease is mechanical and absolute. The decision process in arriving at a referral for surgical correction is often complex and requires consideration of the risk of the procedure itself and the risks of prosthetic heart valves in relation to patient-specific conditions. Therefore the type of mechanical intervention (percutaneous or surgical, repair versus replacement) is a factor in the timing of intervention.

AORTIC STENOSIS

Assessing Stenosis Severity

The severity of aortic stenosis can be assessed noninvasively through echocardiography or invasively during cardiac catheterization.[3] Both methods can provide an accurate assessment of valve area and transaortic gradients. However, because of its ease and accuracy, echocardiography remains the primary modality for the assessment and follow-up of aortic stenosis. In virtually all patients, transthoracic evaluation provides adequate hemodynamic information in the assessment of stenosis severity so that management strategies can be well formulated. Morphologic information (e.g., pattern and degree of calcification, number of cusps), as well as an assessment of ventricular function and hypertrophy, can readily be obtained.

Lesion severity can usually be categorized by the calculation of the aortic valve area and measurement of the mean transvalvular pressure gradient.[4] By echocardiography, the continuity equation can readily be applied to determine valve area with mean gradients measured by Doppler techniques.

$$\mathrm{AVA} = \prod (\mathrm{D}/2)^2 \times \frac{\mathrm{V_{lvot}}}{\mathrm{V_{AV}}}$$

where *AVA* = aortic valve area, *D* = diameter of the left ventricular outflow tract, V_{lvot} is the velocity of blood through the left ventricular outflow tract (LVOT) measured by pulse wave Doppler, and V_{AV} is the maximum velocity across the aortic valve measured by continuous wave Doppler. Accuracy in determining valve area by echocardiography depends on the accuracy of measuring these elements. Calcification can present problems in accurately measuring LVOT diameter. Multiple windows of interrogation that are optimally aligned with blood flow ensure a more precise determination of maximum velocity. Direct planimetry of the aortic valve can be performed through transesophageal echocardiography and correlates well with the Doppler-derived valve area.

If cardiac catheterization is performed, the formula derived by Gorlin and Gorlin[5] is applied to calculate the orifice area.

$$AVA = \frac{CO/SEP(HR)}{44.3(C)\sqrt{MG}}$$

where *AVA* = aortic valve area (cm^2), *CO* = cardiac output (mL/min), *SEP* = systolic ejection period (sec), *HR* = ventricular rate (bpm), and *MG* = mean transvalvular gradient. An accurate cardiac output calculation depends on the appropriate use of thermodilution (which is less accurate with low flow states, significant tricuspid insufficiency, or irregular rhythm); Fick (which requires accurate measurement of oxygen consumption); or angiographic technique.[5] Transducer placement and timing of measurements are important variables in calculating accurate valve areas.

Both techniques to assess valve area depend on flow, so calculated valve areas may be relatively small in the presence of low flow (i.e., low cardiac output) and low pressure gradients. During catheterization, calculation of valve resistance may be helpful in these situations.[6] Aortic valve resistance can be calculated as follows:

$$R_{AV} = [(MG) \times (HR) \times (SEP)] \times 1.33$$

where R_{AV} = aortic valve resistance (dyne-sec-cm^{-5}), *HR* = ventricular rate (bpm), *MG* = mean transvalvular gradient (mm Hg), and *SEP* = systolic ejection period (sec). Because resistance may be less sensitive to changes in flow, higher valve resistance (>250 dyne-sec-cm^{-5}) is generally seen with truly severe aortic stenosis. The use of dobutamine either at cardiac catheterization or coupled with echocardiography may be of benefit in these conditions to help differentiate "pseudo" from true stenosis[7] and is discussed later.

Assuming normal cardiac output, severe aortic stenosis is usually present when mean gradients exceed 40 mm Hg. By echocardiography, this usually corresponds to a peak transaortic velocity that exceeds 4.0 to 4.5 meters per second.[8] Aortic stenosis is considered severe when these values are present or the calculated valve area is less than 1.0 cm.[2] Table 46–1 provides definitions of mild, moderate, and severe aortic stenosis.

Occasionally, noninvasive and invasive measures provide differing results with regard to severity. Aside from technical fidelity in measurement, the phenomenon of pressure recovery may explain some differences. Distal to the stenosis, some of the blood flow kinetic energy may be recovered in pressure, a phenomenon that is more apparent when the ascending aorta is small. In these cases, echocardiographic velocity may be higher and the valve area may appear smaller than that determined at cardiac catheterization. Calculation of an energy loss coefficient echocardiographically by accounting for the size of the proximal ascending aorta may be helpful to reconcile calculated differences.[9,10]

Table 46–1 Measures of Severity in Aortic Stenosis

Severity of Aortic Stenosis	Mild	Moderate	Severe
Doppler jet velocity	<3.0	3.0-4.0	>4.0
Mean gradient (mm Hg)	<25	25-40	>40
Aortic valve area (cm^2)	>1.5	1.0-1.5	<1.0

Overall, pressure gradients and valve areas by echocardiography and cardiac catheterization correlate well with one another such that in most cases, only echocardiography is necessary to define the severity of aortic stenosis. Therefore, unless noninvasive evaluation is ambiguous, cardiac catheterization is used only for the identification of coronary artery disease before aortic valve surgery.

Symptomatic Patients

The timing of surgical intervention in severe aortic stenosis is clear from its natural history. Once symptoms of heart failure, angina, or syncope develop, the prognosis abruptly changes; the 2-year survival of patients presenting with heart failure approaches 50% without surgical correction.[11] No randomized clinical trials are available that compare outcome with medical therapy versus surgical correction in symptomatic patients, but observational data consistently demonstrate that aortic valve replacement is associated with a substantial improvement in overall survival and symptomatology.[12-15] Therefore, it is universally recommended that symptomatic patients with severe aortic stenosis undergo surgical correction.

The outcome and risk of surgery is in part related to left ventricular function.[16] In patients with mild or moderate left ventricular dysfunction, aortic valve replacement confers a similar favorable outcome as do those with normal left ventricular function. Excessive afterload, also called *afterload mismatch,* is the prime cause of the dysfunction in many, if not most, of these patients and is promptly corrected after valve replacement.[17] In those with severely reduced left ventricular function, complete resolution of symptoms and left ventricular dysfunction may not ensue.[18] Despite this, the operative risk of aortic valve replacement appears acceptable and the majority of patients experience improved functional status.[19-23] The presence of coronary artery disease is associated with increased mortality after surgery in patients with severely decreased LVEF[24]; this suggests that afterload mismatch is not the primary cause of ventricular dysfunction in these patients.

Low-Gradient Aortic Stenosis

Patients with severe aortic stenosis (AVA < 1.0 cm^2) may present with low transvalvular pressure gradients (mean gradient < 30 mm Hg) in the setting of severe left ventricular dysfunction.[25] This nominal discrepancy, occurring in the presence of low transvalvular flow, may be seen in patients with primary contractile dysfunction or excessive afterload, or some combination of the two. In those with truly severe stenosis, the use of low-dose dobutamine infusion generally produces an increase in flow and an increase in the transvalvular pressure gradient with little or no change in the valve area. By contrast, a "pseudostenosis" may be related to the reduced valve-opening force that is caused by the weakened ventricle. In this situation dobutamine infusion augments valve opening; there is an increase in transvalvular flow with little or no change in the pressure gradients, and the calculated effective valve area increases. Dobutamine infusion also provides important information about left ventricular contractile reserve. Thus, a limited contractile reserve (i.e., stroke volume

increment is < 25% during dobutamine infusion) identifies the patient with a severe contractile deficiency and a poor prognosis, regardless of medical or surgical treatment.[26]

Elderly Patients

Calcific aortic stenosis is the most common valvular lesion seen in elderly patients. The indications for surgery are the same as for younger patients. Although advanced age has been shown to be a determinant of outcome, it does not preclude surgery because the majority of elderly patients have a good outcome following surgery. For example, in a large retrospective study of 1100 patients aged older than 80 years undergoing aortic valve replacement, 30-day cardiac and all-cause mortality rates were 4% and 6.6%, respectively.[27] Overall, elderly patients experience an improvement in function and quality of life to a degree that is similar to age-matched controls.[28-32]

Elderly patients may present with anatomic features that may necessitate further surgical consideration.[28,33] For example, elderly women may have narrow outflow tracts and smaller aortic annular dimensions. This may require annular dilatation to allow for a larger prosthesis or occasionally require a composite graft. In addition, heavy calcification is not uncommon and may require extensive débridement. Comorbidities and the patient's wishes and expectations must be considered.

Role of Percutaneous Intervention

Percutaneous balloon dilatation of the stenotic aortic valve plays a pivotal role in the very young with congenital lesions.[34] However, aortic balloon valvotomy plays a limited role in adult patients with severe calcific disease.[35] In adults the morbidity and mortality rates are high, with reported in-hospital mortality rates between 3.5% and 13.5%.[36] Furthermore, the durability of the procedure is limited because most patients experience recurrence within 6 months to 1 year.[37] Although the procedure has been used as a bridge to surgery, data supporting this are limited; under most circumstances, direct operative replacement is more appropriate.

Asymptomatic Patients

Aortic valve replacement in asymptomatic patients with severe stenosis is controversial. Despite limited data, some experts advocate earlier surgery, arguing that irreversible myocardial damage and fibrosis may ensue during the absence of symptoms, and that a finite risk for sudden death exists during this time period.[38] However, the risk of sudden death in an asymptomatic patient is < 1% per year.[39] Several factors identify asymptomatic patients who may be at particular risk without surgical correction.[39] These include patients with an abnormal response to exercise, abnormal systolic function, ventricular arrhythmias, or marked hypertrophy with hyperdynamic function, and those with a combination of marked valvular calcification, a peak jet velocity of > 4 m/sec and evidence of rapid progression (i.e., an increase in jet velocity > 0.3 m/sec within 1 year).[40-43] With this approach, the risk of surgery and the attendant long-term prosthesis risks must be weighed. Apart from perioperative complications, implantation of a prosthesis is associated with a significant annual complication rate.[44] Therefore, the risk of valve replacement likely exceeds benefit in those who are truly asymptomatic with normal left ventricular function. Many, if not most, patients with the previously mentioned risk factors will develop symptoms after a brief period and will then qualify for prompt surgical correction.

Progression to symptomatic disease is common in patients with severe stenosis, with a reported incidence of 14% at 1 year and 38% at 2 years.[45] In addition, faster progression of disease is more likely in those with concomitant coronary disease, significant calcification of the valve, and in those older than 50 years of age.[42] The rate of progression has been linked to adverse outcomes, particularly in those with an increase in Doppler velocities > 0.3 m/sec or a decrease in valve area greater than 0.1 cm^2 per annum.[40] Thus, regular monitoring is warranted in asymptomatic patients with severe stenosis. Regardless of symptoms, patients who undergo other valve surgery or coronary bypass generally undergo aortic valve replacement at the same time.

Role of Exercise Testing

Exercise testing has been proposed as a method of risk stratification in patients with severe aortic stenosis but without clear symptomatology.[46] It should not be performed in those whose symptoms are attributable to aortic stenosis. However, with close physician supervision, exercise testing can be considered and may uncover exercise-induced symptoms and intolerance. The presence of exercise-induced hypotension portends a poor prognosis. In a study of 66 asymptomatic patients with severe aortic stenosis but without angiographic coronary artery disease followed for a mean of 15 months, four patients died suddenly, with all four having an abnormal test.[47,48]

Overall Approach

Surgical correction should be performed in all patients with symptomatic severe aortic stenosis (Table 46–2). Aortic valve replacement has been associated with marked improvements in morbidity and mortality rates across numerous symptomatic subgroups. In general, patients with only moderate aortic stenosis and symptoms resembling those of aortic stenosis do not require surgical intervention; other causes for symptoms should be sought. With rare exception, valve replacement should not be performed in truly asymptomatic patients. Asymptomatic patients with high-risk features require close monitoring. Figure 46–1 provides an algorithmic approach incorporating these recommendations.[25]

MITRAL STENOSIS

Assessment of Severity

Echocardiography is the preferred modality to assess for the presence and severity of mitral stenosis.[49] Classic doming of the anterior leaflet is readily identified from 2-D images, as are other morphologic features important in the assessment of mitral stenosis. Doppler techniques are used to measure the transmitral pressure gradients using the modified Bernoulli equation, as well as to calculate the mitral valve area (MVA)

using the diastolic pressure half-time method or the continuity equation. These measures correlate well with valve areas that are derived at cardiac catheterization.[50] The pressure half-time method should not be used when significant aortic regurgitation is present or immediately after mitral valvotomy because abnormalities of atrial or ventricular compliance can affect MVA calculation.[51] Other techniques may be used to calculate MVA including the proximal isovolumetric surface area (PISA) method, as well as direct planimetry.[52] Importantly, pulmonary artery pressures should be determined to aid in the hemodynamic assessment.

Morphologic assessment of the mitral apparatus provides important information that may help guide the type of mechanical intervention (i.e., percutaneous balloon mitral valvuloplasty, surgical commissurotomy, or valve replacement). Echocardiography provides an assessment of leaflet mobility, thickness, calcification, and subvalvular thickening. When leaflets are relatively mobile, noncalcified, and with little subvalvular involvement, percutaneous mitral balloon valvuloplasty (PMBV) is generally successful and provides a safe and effective nonsurgical approach.[53] An echocardiographic scoring system described by Wilkins[54] combines these factors into a useful approach to predict procedural success (Table 46–3). The degree of commissural calcification has also been used to help identify the most appropriate candidates for PMBV.[55,56] Higher scores indicate more severe disease and predict a lower likelihood of procedural success of PMBV. A similar scoring system has been described to predict the likelihood of postprocedural severe mitral regurgitation.[57] When patients have significant mitral abnormalities (score > 10), the sensitivity and specificity for predicting severe mitral regurgitation is 82% and 91%, respectively. Finally, higher echocardiographic morphologic scores have been related to higher inpatient costs.[58]

Hemodynamic measurements during cardiac catheterization can be performed when noninvasive findings are ambiguous or discordant with clinical findings. Transmitral pressure gradients can be measured, and the MVA can be calculated using the Gorlin hydraulic formula.[59] Pulmonary pressures and resistance are routinely obtained to assess the hemodynamic effect of the stenosis on the pulmonary circulation. When pulmonary artery balloon occlusion or wedge pressure is used as a surrogate for left atrial pressure, the transmitral pressure gradient may be overestimated despite adjustment for phase delay. Transseptal puncture is therefore more appropriate in determining the pressure gradient, especially if the accuracy of the wedge pressure is questioned.[60] Left ventriculography is used to assess for the presence of significant mitral insufficiency, and coronary angiography is performed if intervention is contemplated.

The resting mitral valve area and mean pressure gradient are used to categorize the severity of mitral stenosis (Table 46–4). Not infrequently, however, the patient's symptoms may be out of proportion to the severity of the stenosis in the basal or resting state. In these cases assessment of hemodynamics with exercise at catheterization or coupled with

Table 46–2 Recommendations for use of Aortic Valve Replacement in Patients with Aortic Stenosis

Aortic Valve Replacement Indicated

- Patients with severe aortic stenosis and symptoms (angina, syncope, or heart failure)
- Patients with severe or moderate aortic stenosis who are undergoing coronary artery bypass graft surgery or surgery on the aorta or other heart valves

Aortic Valve Replacement Possibly Indicated

- Asymptomatic patients with severe aortic stenosis and at least one of the following:
  - Ejection fraction < 50%
  - Hemodynamic instability during exercise (e.g., hypotension)
  - Ventricular arrhythmia

*Aortic valve replacement is not indicated to prevent sudden death in asymptomatic patients with none of the findings listed. Modified from Carabello BA: Clinical practice. Aortic stenosis. N Engl J Med 2002;346:677-82.

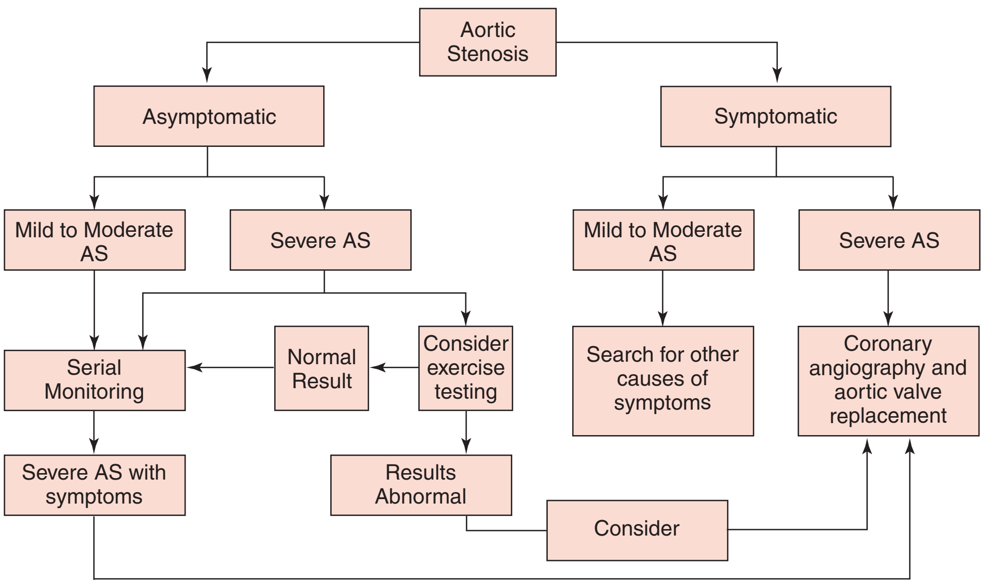

Figure 46–1 Algorithm for the timing of surgery in patients with aortic stenosis.

echocardiography can help clarify the physiologic burden of mitral stenosis.[61] If a significant rise in mean transmitral pressure gradient (>15 mm Hg) or pulmonary capillary wedge pressure (> 25 mm Hg) is observed or if pulmonary hypertension results (systolic pressure > 60 mm Hg), then percutaneous intervention should be considered if valve morphology is appropriate.[62] Therefore, an assessment of severity with exercise can help resolve clinical discrepancies in severity, as well as aid in planning for mechanical intervention.

Table 46–3 Echocardiographic Classification of Mitral Valve Anatomy

Leaflet Mobility
1. Highly mobile valve with restriction confined to the leaflet tips
2. Middle portion and base of leaflets with reduced mobility
3. Valve leaflets move forward in diastole mainly at the base
4. No or minimal forward movement of the leaflets in diastole

Valvular Thickening
1. Leaflets near normal (4-5 mm)
2. Midleaflet thickening, marked thickening of the margins
3. Thickening extends through the entire leaflets (5-8 mm)
4. Marked thickening of all leaflet tissue (>8-10 mm)

Subvalvular Thickening
1. Minimal thickening of chordal structures just below the valve
2. Thickening of chordae extending up to one third of chordal length
3. Thickening extending to the distal third of the chordae
4. Extensive thickening and shortening of all chordae extending down to the papillary muscle

Valvular Calcification
1. A single area of increased echo brightness
2. Scattered areas of brightness confined to leaflet margins
3. Brightness extending into the midportion of leaflets
4. Extensive brightness through most of the leaflet tissue

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Percutaneous Mitral Balloon Valvuloplasty

Percutaneous mitral balloon valvuloplasty (PMBV) was first used approximately 20 years ago using a double balloon technique.[63] Today most centers use a single balloon (Inoue balloon) that is advanced across the interatrial septum into the left atrium and across the mitral valve.[64] The balloon is inflated across the stenotic valve and produces separation of the fused commissures, as well as fracture of calcific leaflet tissue similar to surgical commissurotomy. A retrograde non-transseptal technique and a metallic valvotomy technique have also been used with acceptable results.[65,66] The procedure is performed in many centers with concomitant transesophageal or intracardiac echocardiography to guide the procedure and monitor for complications.[2]

Patients are selected for PMBV on the basis of hemodynamic and echocardiographic parameters. PMBV should be considered only in those without significant mitral insufficiency or evidence of left atrial appendage thrombus. These can readily be excluded by transesophageal echocardiography before catheterization.[67] Those with low echocardiographic scores are the most appropriate candidates for the procedure because these low scores have been shown to predict procedural success and complications.[68]

The efficacy of PMBV appears to be good and is comparable with surgical open commissurotomy.[69,70] Acutely, PMBV produces a significant increase in MVA and significant decreases in left atrial pressure and transmitral gradient. The morphology of the mitral apparatus is the most important factor in determining outcome, with postprocedural hemodynamics being important predictors of longer-term clinical outcome.[71] Complications include severe mitral insufficiency; residual atrial septal defect; and, less frequently, left ventricular perforation and embolism.[36] In experienced centers the mortality rate is reported to be less than 1%.[72] Given the safety and efficacy of this nonsurgical technique, it is the preferred method of mechanical correction of mitral stenosis.

PMBV is appropriate in symptomatic patients with moderate-to-severe mitral stenosis or asymptomatic patients

Table 46–4 Grades of Mitral Stenosis Severity

Severity	MVA, cm^2	Gradient, mm Hg	PAP	Symptoms	Signs	Therapy
Mild	>1.8	2-4	Normal	Usually absent	S_2-OS >120 ms; normal P_2	IE prophylaxis
Moderate	1.2-1.6	4-9	Normal	Class I-II	S_2-OS 100-120 ms; normal P_2	IE prophylaxis; diuretics
Moderate to severe	1.0-1.2	10-15	Mild pulmonary HTN	Class II-III	S_2-OS 80-100 ms; P_2 increase	IE prophylaxis; BMV if applicable or surgery
Severe	<1.0	>15	Mild-to-severe pulmonary HTN	Class II-IV	S_2-OS < 80 ms; P_2 increase; RV lift Sx if R heart fails	IE prophylaxis; BMV or surgery

BMV, balloon mitral valvuloplasty; HTN, hypertension; IE, infective endocarditis; MVA, mitral valve area; OS, opening snap; PAP, pulmonary artery pressure;
RV, right ventricular; Sx, symptoms.
Modified from *Circulation* 2005;112:432-437

Table 46–5 Mechanical Therapy for Mitral Stenosis

Procedures	Indications	Contraindications	Advantage	Disadvantages
Balloon valvuloplasty	Sx; MVA < 1.5 cm^2 with good valve score	MVA > 1.5 cm^2	Percutaneous	Reduced applicability with poor valve morphology
	Pulmonary HTN, MVA < 1.5 cm^2 with good valve score Sx or pulmonary HTN + high-risk surgery and any valve score.	LA thrombus More than moderate MR		
Open commissurotomy	Sx, MVA < 1.5 cm^2; pulmonary HTN with MVA < 1.5 cm^2	MVA > 1.5 cm^2	Avoids prosthetic valve	Risks of surgery and limited applicability
Mitral valve repair	Sx, MVA < 1.5 cm^2 or pulmonary HTN with MVA < 1.5 cm^2	MVA > 1.5 cm^2	Applicable when BMV and open commissurotomy fail	All the risks of surgery and of a prosthesis

BMV, balloon mitral valvuloplasty; HTN, hypertension; LA, left atrial; MR, mitral regurgitation; MVA, mitral valve area; Sx, symptoms.
Modified from Carabello BA: Modern management of mitral stenosis. Circulation 2005;112:432-7.

with resting pulmonary hypertension or adverse hemodynamics on exercise. It should also be considered in asymptomatic women planning on childbearing to obviate complications during pregnancy.[73] Contraindications for PMBV have been published (Table 46–5).

Overall Approach

In asymptomatic patients, percutaneous mechanical intervention is not generally entertained unless hemodynamic abnormalities coexist with at least moderate stenosis (Fig. 46–2).[74] Thus, if resting pulmonary hypertension exists (>50 mm Hg) or exercise testing reveals exercise intolerance, induced pulmonary hypertension (>60 mm Hg), or high pulmonary artery wedge pressures (>25 mm Hg), then PMBV should be considered, although confirmatory data supporting this approach are not available.

Symptomatic patients with moderate or severe mitral stenosis (MVA < 1.5 cm^2) are generally considered for PMBV if valve morphology is favorable and significant mitral insufficiency and left atrial thrombus are excluded (Figs. 46–3 and 46–4).[75] If hemodynamically mild mitral stenosis is present at rest in the presence of symptoms, then exercise testing should be employed to assess for adverse hemodynamics during stress. If pulmonary hypertension or high pulmonary artery wedge pressure is observed, other problems (e.g., left ventricular dysfunction) should be considered. If a significant increase in transmitral gradient is observed, then PMBV is considered. When patients are severely symptomatic (New York Heart Association [NYHA] class III-IV) and conditions are not favorable for percutaneous intervention, then referral for mitral valve surgery is recommended. These include patients with significant mitral insufficiency (3 to 4+) or heavily calcified valves that would predict adverse periprocedural and clinical outcomes.

If left atrial or left atrial appendage thrombus is present, but conditions otherwise favor PMBV, a period of anticoagulation can be advocated in order to assist a later attempt at PMBV.[76] Percutaneous intervention may be feasible after several months of anticoagulation as long as thrombus resolution or organization is confirmed by echocardiography.

Surgical approaches to mitral stenosis are used when PMBV is not favorable or is unavailable. Mitral valve replacement or open commissurotomy is usually employed (see Table 46–5). Patients at high risk for surgery can be considered for PMBV even though they may not be optimal candidates for the percutaneous procedure.[77] Recurrent stenosis can either be managed with repeat PMBV or mitral valve replacement.[78,79] The risks of each should be considered given patient comorbidities and valve morphology.

AORTIC INSUFFICIENCY

Assessment of Severity

The severity of aortic insufficiency can be assessed by Doppler echocardiography. Color flow and spectral Doppler imaging provide the foundation for the determination of the severity of insufficiency. An integrative approach is usually applied using all information from the echocardiography study to arrive at a coherent assessment. This should routinely include a 2-D assessment of the aortic valve, aorta, and left ventricular chamber size and function.

Color flow imaging of the regurgitant jet provides important clues to severity. The length alone of the color jet in the left ventricle during diastole is a limited measure of severity; its width and area in the parasternal views are more reliable indicators of regurgitant severity. In addition, the size of the vena contracta provides a useful measure of severity when its size exceeds 6 mm.[80] The vena contracta is the narrowest central flow portion of any color flow jet. It is essentially the smallest jet size measured at the level of the aortic valve in aortic regurgitation. With these measures, the larger the width or area, the greater the severity of regurgitation. Supportive signs of severe aortic regurgitation include a short pressure half-time of the aortic regurgitant signal, holodiastolic flow reversal in the descending thoracic aorta, and at least

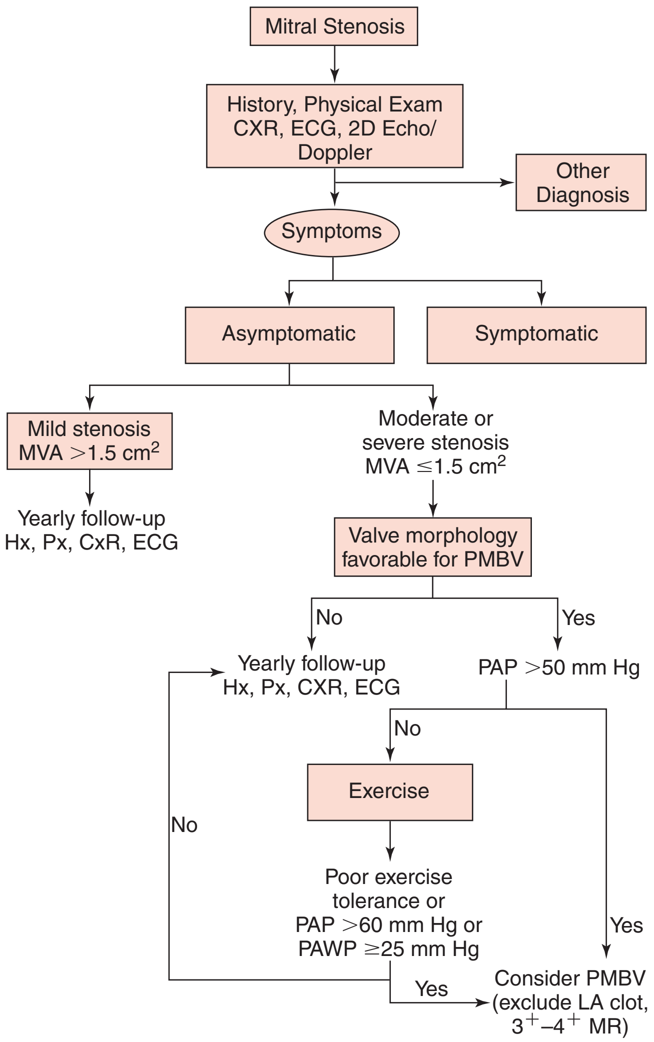

Figure 46–2 Management strategy for asymptomatic patients with mitral stenosis. CXR, Chest r-ray; LA, left atrial; MVA, mitral valve area; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PMBV, percutaneous mitral balloon valvuloplasty. (Redrawn from ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on Management of Patients with Valvular Heart Disease]. J Am Coll Cardiol 1998;32:1486-588.)

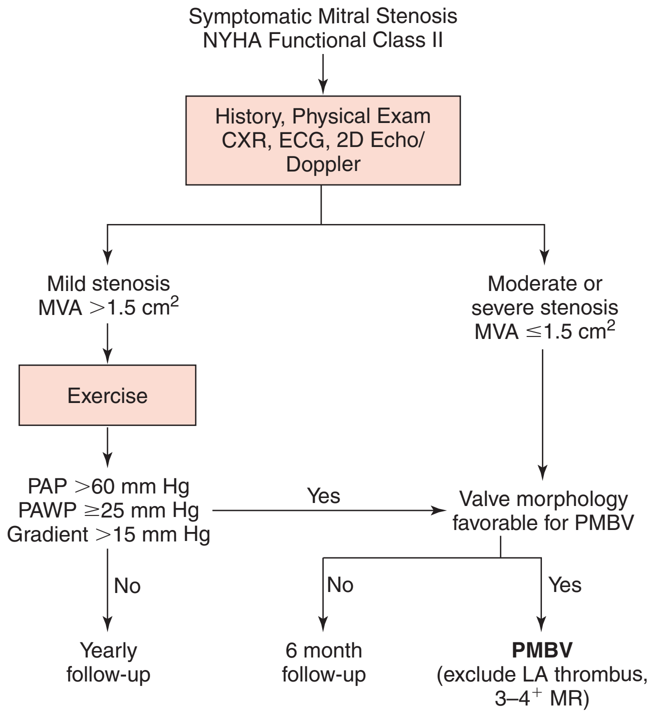

Figure 46–3 Management strategy for patients with mitral stenosis and mild symptoms. CXR, Chest x-ray; LA, left atrial; MVA, mitral valve area; PMBV, percutaneous mitral balloon valvuloplasty; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure. (Redrawn from ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on Management of Patients with Valvular Heart Disease]. J Am Coll Cardiol 1998;32:1486-588.)

moderate LV enlargement.[81] Parameters for the diagnosis of severe aortic regurgitation by echocardiography have been published (Table 46–6).

The aforementioned measures provide a qualitative or semiquantitative measure of severity. The flow convergence method or proximal isovelocity surface area (PISA) can be applied, but there is considerably less experience with PISA in aortic regurgitation compared with its use in mitral insufficiency.[82] Using this method, the size of the regurgitant orifice can be calculated and an assessment of regurgitant volumes and severity can be made. A similar volumetric assessment[83] can be made by comparing aortic stroke volume (i.e., TVI of LV outflow) with that of another uninvolved valve (usually mitral or pulmonic valve).

Hemodynamic assessment at cardiac catheterization is used when noninvasive techniques fail to provide confident results.[59] Qualitative assessment of severity is made by assessing the persistence of opacification of the left ventricle during diastole and comparing this with aortic opacification (Table 46–7). Quantitative left ventriculography can be employed to calculate regurgitant volumes and regurgitant fraction. Total stroke volume can be obtained by a careful angiographic assessment of end diastolic and end systolic volumes. When forward stroke volume (obtained from thermodilution or Fick cardiac output techniques) is subtracted from total stroke volume, regurgitant volume is derived.

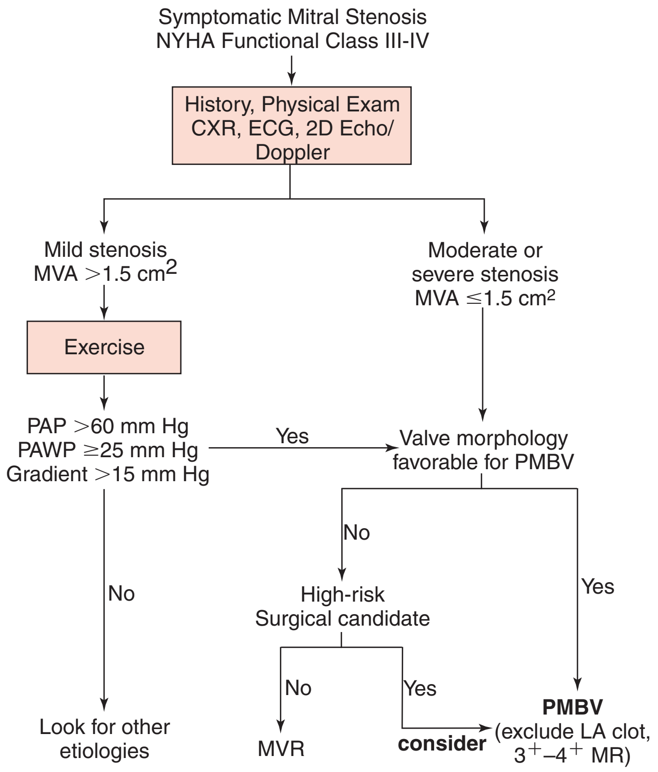

Figure 46–4 Management strategy for patients with mitral stenosis and moderate to severe symptoms. CXR, Chest x-ray; LA, left atrial; MVA mitral valve area; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PMBV, percutaneous mitral balloon valvuloplasty. (Redrawn from ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on Management of Patients with Valvular Heart Disease]. J Am Coll Cardiol 1998;32:1486-588.)

Further division by the total stroke volume results in the regurgitant fraction. A regurgitant fraction exceeding 50% is consistent with severe aortic insufficiency. Coronary angiography is performed to assess the status of the coronary arteries in those at risk before surgical intervention.

Timing of Surgical Intervention

As with other cardiac valves, recommendations are largely based on observational data in relatively small populations because prospective and adequately powered clinical trials have not been performed. Despite this, robust data are available that favor surgical intervention on the basis of the presence of severe insufficiency, symptoms, and the size and function of the left ventricle. The vast majority of patients with aortic insufficiency undergo valve replacement, although experience with valve repair is accumulating in selected patient populations.

Symptomatic Patients with Normal Left Ventricular Function

The prognosis of patients with significant aortic insufficiency has been shown to be related to the presence of heart failure symptoms. In a study encompassing 246 patients followed conservatively with severe or moderately severe insufficiency, those with NYHA class III or IV heart failure had an annual mortality rate of 25%, whereas those with class II heart failure had an annual mortality rate of 6%.[84] Surgery significantly reduced the overall cardiovascular mortality rate. The presence of significant symptoms of heart failure or angina in other studies indicates high annual mortality rates (>10%) in those treated conservatively.[85,86]

Aortic valve surgery is indicated in patients with normal left ventricular function when NYHA class III or IV heart failure symptoms are present.[87] However, when milder symptoms are present, it is often unclear whether symptoms are cardiac in origin. Exercise stress testing may provide helpful information in such patients.[88] However, when marked left ventricular enlargement (exceeding 75 mm at end-diastole) is present or when ejection fraction (EF) is borderline (EF 50% to 55%), the presence of even mild symptoms should prompt a consideration of surgical correction.

The aforementioned applies chiefly to patients with chronic aortic insufficiency. Patients with acute severe insufficiency invariably present with advanced symptomatology (pulmonary edema or cardiogenic shock, or both) and often have normal left ventricular systolic function, tachycardia, and normal left ventricular chamber sizes. In these settings, compensatory mechanisms are often inadequate, and poor outcomes are seen without prompt surgical intervention. Therefore nearly all patients with symptomatic severe aortic insufficiency, whether chronic or acute, should be considered candidates for surgical correction.[89]

Symptomatic Patients with Left Ventricular Dysfunction

Surgical correction of symptomatic severe aortic insufficiency usually produces improvement in symptoms irrespective of the state of the left ventricle. In a small study of symptomatic patients with a mean preoperative EF of 45%, the majority had a decrease in symptoms and a postoperative increase in left ventricular function (mean postoperative EF 59%).[90] Likewise, symptomatic patients with mild or moderate left ventricular dysfunction also benefit from corrective aortic valve surgery. Patients with severe LV dysfunction and/or class IV symptoms have increased mortality rates and less chance of complete functional recovery postoperatively.[91] These patients often present difficult management issues as irreversible ventricular dysfunction may be present. Although perioperative risk is high in such patients, aortic valve surgery often provides a better alternative than medical therapy alone. In a study from the Mayo Clinic involving 450 patients who underwent aortic valve surgery for chronic aortic insufficiency, approximately 10% had left ventricular ejection fractions below 35%. In such patients, operative mortality was 14%. However, the LVEF increased by 4.9 percentage units after surgery and most patients had prolonged survival without progression to heart failure. Thus, even though a controlled trial has not been performed, it can be recommended that

Table 46–6 Echocardiographic Grading of Aortic Regurgitation

	Mild	Moderate		Severe
Specific signs for AR severity	Central jet width < 25% of LVOT Vena contracta < 0.3 cm* No or brief early diastolic flow reversal in descending aorta	Signs of AR > mild present, but no criteria for severe AR		Central jet width ≥ 65% of LVOT Vena contracta >0.6 cm*
Supportive signs	Pressure half-time > 500 ms Normal LV size†	Intermediate values		Pressure half-time < 200 ms Holodiastolic aortic flow reversal in descending aorta Moderate or greater LV enlargement‡
Quantitative parameters§		Mild-to-moderate	Moderate-to-severe	
R Vol (mL/beat)¶	< 30	30-44	45-59	≥60
RF (%)	< 30	30-39	40-49	≥50
EROA (cm^2)¶	<0.10	0.10-0.19	0.20-0.29	≥0.30

*At a Nyquist limit of 50-60 cm/sec.
†LV size applied only to chronic lesions. Normal 2-D measurements: LV minor-axis < 2.8 cm/m^2.
‡In the absence of other etiologies of LV dilatation.
§Quantitative parameters can help subclassify the moderate regurgitation group into mild-to-moderate and moderate-to-severe regurgitation as shown.
Caution should be used when interpreting non-normalized volumes in isolation.
¶Consider body size (BSA).
AR, aortic regurgitation; *EROA*, effective regurgitant orifice area; *LV*, left ventricular outflow tract; LVOT, left ventricular outflow tract; *RF*, regurgitant fraction; *R Vol*, regurgitant volume.
From Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.

Table 46–7 Qualitative Grading of Aortic Regurgitation at Cardiac Catheterization

Grade	Description
1+	Incomplete, faint left ventricular opacification that clears with systole
2+	Faint, complete left ventricular opacification not completely cleared with each systole
3+	Progressive opacification such that the left ventricle equals the density of aortic root
4+	Left ventricular opacification on the first or second diastole greater than aortic root

such patients should not be denied the potential benefits of surgery.[92] A period of intense medical treatment to relieve the signs and symptoms of heart failure is warranted prior to surgical correction.

Asymptomatic Patients

Some controversy exists regarding surgery for severe aortic regurgitation among asymptomatic individuals, particularly when left ventricular systolic function is normal. Left ventricular size by echocardiography at end diastole and end systole has been recommended as a guide for recommending surgical intervention. Severe LV dilatation (LV end diastolic dimension > 75 mm) or systolic dysfunction (LV end systolic dimension > 55 mm) appears to represent high-risk patients with an increased incidence of adverse outcomes without intervention.[93,94] Despite the lack of large-scale studies evaluating patients with asymptomatic severe aortic insufficiency, conventional wisdom indicates that LV ejection fraction and end systolic dimension are important predictors of survival and left ventricular function following surgical correction.[94] Thus, an EF < 50% or an ESD > 55 mm, or both, can be considered an indication for AVR in an asymptomatic patient. However, patients with moderately severe dilatation (LV end diastolic dimension > 70 to 75 mm) have been shown to have acceptable outcomes with conservative management.[95] This suggests that end-diastolic size alone is not a strong indication for aortic valve replacement.

Serial monitoring is required in patients with severe aortic insufficiency who do not yet meet criteria for surgical correction and remain asymptomatic.[96] Patients with a declining ejection fraction represent a subgroup at higher risk, and regular monitoring is mandatory.[97] In addition, some patients who develop systolic dysfunction do so without premonitory symptom development.[98] Therefore, in addition to serial follow-up for symptom evaluation, objective evidence by echocardiography is invaluable to identify asymptomatic patients with left ventricular dysfunction when surgical intervention is appropriate.

Overall Approach

An algorithm to guide timing of surgery in severe chronic aortic insufficiency has been developed (Fig. 46–5).[93] In essence, all patients with symptoms (functional class III or IV) or with LV dysfunction irrespective of symptoms should undergo corrective aortic valve surgery. Serial noninvasive

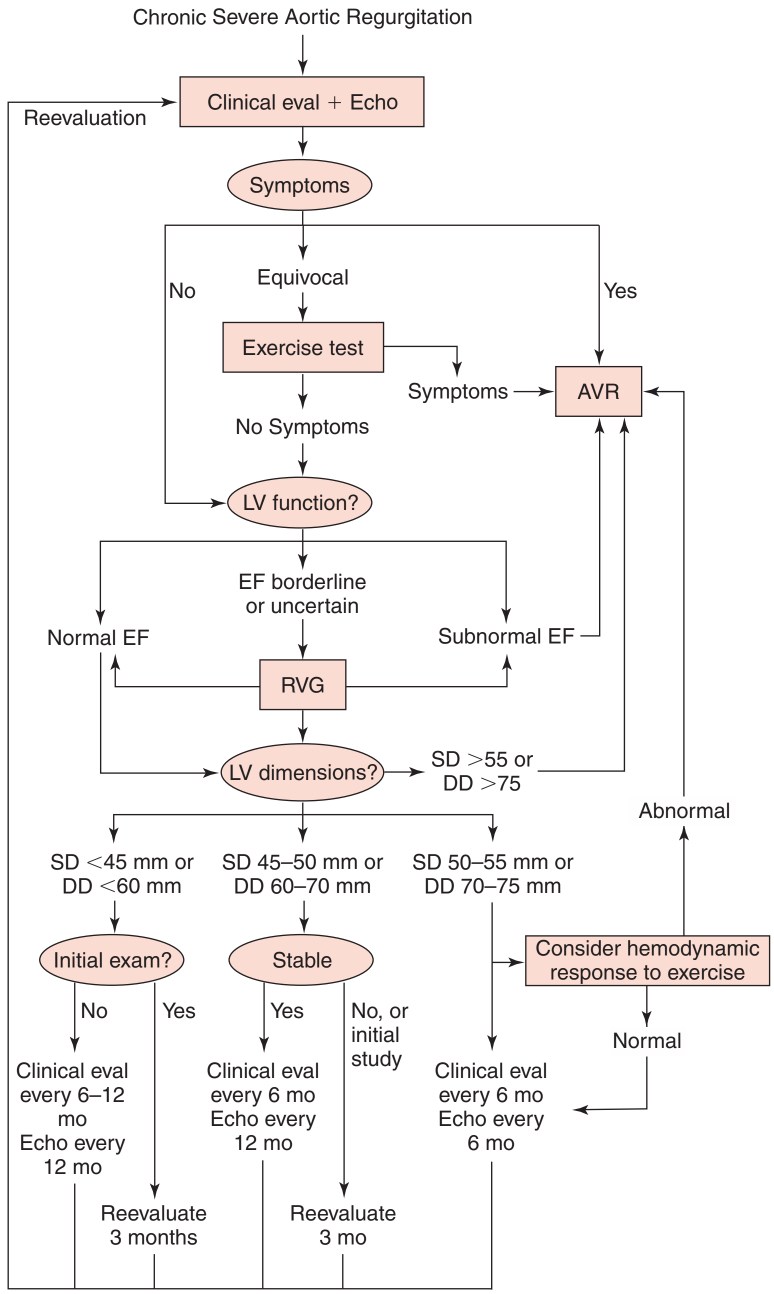

Figure 46–5 Timing of surgery for aortic regurgitation. DD, end-diastolic dimension; RVG, radionuclide ventriculography; SD, end-systolic dimension. (Redrawn from ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on Management of Patients with Valvular Heart Disease]. J Am Coll Cardiol 1998;32:1486-588.)

monitoring is mandatory for those asymptomatic patients without resting ventricular dysfunction or who are not yet candidates for correction.

MITRAL INSUFFICIENCY

Assessment of Severity

An integrative approach is recommended when using echocardiography to assess the severity of mitral regurgitation.[81] The combination of 2-D, color, and spectral Doppler measurements, as well as quantitative parameters, will aid in identifying severe mitral regurgitation in a more accurate and reproducible fashion. An application of specific and supportive parameters in mitral regurgitation is shown in Table 46–8. It should be recognized that chronic severe mitral insufficiency rarely exists without left ventricular enlargement, and therefore the presence of severe chronic mitral insufficiency should be questioned if the left ventricle is not enlarged. Likewise, the diagnosis of chronic severe mitral insufficiency should be questioned if left atrial enlargement is not present.

Color flow Doppler parameters can help to identify severe mitral insufficiency. As a guide to severity, regurgitant jet area lacks accuracy, especially when the jet is eccentric, and should

Table 46–8 Echocardiographic Grading of Mitral Regurgitation

	Mild	Moderate		Severe
Specific signs of severity	Small central jet < 4 cm^2 or < 20% of LA area*	Signs of MR > mild present, but no criteria for severe MR		Vena contracta width > 7 cm with large central MR jet (area > 40% of LA) or with a wall-impinging jet of any size, swirling in LA*
	Vena contracta width < 0.3 cm			Large flow convergence†
	No or minimal flow convergence†			Systolic reversal in pulmonary veins
				Prominent flail MV leaflet or ruptured papillary muscle
Supportive signs	Systolic dominant flow in pulmonary veins	Intermediate signs/findings		Dense, triangular CW Doppler MR jet
	A-wave dominant mitral inflow‡			E-wave dominant mitral inflow (E > 1.2 m/sec)‡
	Soft density, parabolic CW Doppler MR signal			Enlarged LV and LA size§ (particularly when normal LV function is present)
	Normal LV size¶¶			
Quantitative parameters§		Mild-to-moderate	Moderate-to-severe	
R Vol (mL/beat)**	< 30	30-44	45-59	≥60
RF (%)	< 30	30-39	40-49	≥50
EROA (cm^2)**	< 0.20	0.20-0.29	0.30-0.39	≥0.4

*At a Nyquist limit of 50-60 cm/sec.
†Minimal and large flow convergence defined as a flow convergence radius of < 0.4 cm and ≤ 0.9 cm for central jets, respectively, with a baseline shift at a Nyquist of 40 cm/sec; cut-offs for eccentric jets are higher and should be angle corrected.
‡Usually older than 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated LA pressure.
§In the absence of other etiologies of LV and LA dilatation and acute MR.
¶¶LV size applied only to chronic lesions. Normal 2-D measurements: LV minor axis ≤ 2.8 cm/m^2, LV end-diastolic volume ≤ 82 mL/m^2, maximal LA antero-posterior diameter ≤ 2.8 cm/m^2, maximal LA volume ≤ 36 mL/m^2.
¶Quantitative parameters can help subclassify the moderate regurgitation group into mild-to-moderate and moderate-to-severe as shown. Caution should be used when interpreting non-normalized volumes in isolation.
**Consider body surface area (BSA).
CW, continuous wave; EROA, effective regurgitant orifice area; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; RF, regurgitant fraction; R Vol, regurgitant volume.
Modified from Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.

not be used as a single measure of severity.[99] However, significant MR is likely present when large jets penetrate the pulmonary veins and systolic flow reversal is seen. Measurement of the vena contracta may provide a more specific sign of severity, especially when measurements exceed 0.6 to 0.8 cm in long axis views.[100,101] Clinicians should avoid making this measurement in the apical two-chamber view, as the vena contracta may be erroneously wide along the coaptation margins. Although measurement of the vena contracta works well with central or eccentric jets, multiple jets create fundamental problems with this technique.

Spectral Doppler measurements provide important adjunctive information to indicate severe mitral regurgitation. Pulmonary vein systolic flow reversal is a specific sign of hemodynamically severe regurgitation when seen in more than one pulmonary vein.[102] This finding is more reliable in acute or subacute than in chronic mitral insufficiency (it depends on left atrial compliance and other factors). The height of the mitral E velocity is greater than the A wave velocity in severe MR and is usually greater than 1.2 cm/sec. An A wave dominant pattern virtually excludes severe mitral insufficiency.[103] Other supportive information of severe insufficiency is a dense, triangular, early peaking, mitral-insufficient envelope on continuous wave Doppler sampling.

Quantitative methods can be used to assess the severity of mitral insufficiency. Calculation of stroke volumes in a similar manner as described earlier for aortic regurgitation enable one to calculate regurgitant volume, regurgitant fraction, and regurgitant orifice area. Studies confirm the validity of this method to assess the severity of mitral insufficiency.[104] The proximal isovelocity surface area (PISA) method has been validated and appears to be most accurate with central jets arising from circular orifices.[104] Regurgitant flow and an effective regurgitant area (EROA) can be derived. An EROA > 0.4 cm^2 is consistent with severe mitral insufficiency.

Hemodynamic evaluation at cardiac catheterization is used when clinical and noninvasive measures are disparate or inconclusive. Semiquantitative and quantitative measures are

Table 46–9 Qualitative Grading of Mitral Regurgitation at Cardiac Catheterization

Grade	Description
1+	Contrast enters the left atrium without complete chamber opacification
2+	Compete opacification of left atrium; not as dense at left ventricle
3+	Progressive and complete opacification of the left atrium equal in density to left ventricle
4+	Early opacification with the left atrium denser than left ventricle, often with opacification of the pulmonary veins

used to assess for severe insufficiency.[59] A qualitative scheme is shown in Table 46–9. In a manner similar to that described for aortic insufficiency, regurgitant volumes and fraction can be derived with regurgitant fractions exceeding 50%, signifying severe mitral insufficiency.

Timing of Intervention

As with other valvular lesions, there is a paucity of large-scale randomized trials, and recommendations regarding the optimal time of surgery have been largely based on observational data regarding predictors of outcome. Several factors predicting adverse outcomes have been borne out of these data and include end-systolic dimension, ejection fraction, and the presence of atrial fibrillation.[41] Other measures of severe mitral insufficiency (i.e., effective regurgitant orifice area) have been prospectively evaluated and may help refine the definition of an optimal time for surgery.[105]

The etiology of severe mitral insufficiency appears to affect prognosis. Those having primary leaflet abnormalities appear to have a more favorable outcome with surgical intervention. By contrast, those with secondary insufficiency tend to have a prognosis that primarily depends on the underlying process. For example, ischemic or functional mitral insufficiency is associated with higher operative mortality, decreased survival, and a higher incidence of heart failure postsurgery.[106] Here, our discussion centers on chronic mitral insufficiency originating from organic leaflet dysfunction.

Surgical Intervention

Modern surgical methods generally involve either mitral valve replacement with preservation of the subvalvular apparatus or mitral valve repair (see Chapter 47).[107] When mitral valve replacement is performed, removal of the chordal apparatus is no longer performed, if at all possible. When the subvalvular apparatus is preserved during surgical replacement, postoperative left ventricular function and survival are significantly improved compared with the result obtained when the mitral apparatus is disrupted.[108,109] It appears that preservation of the mitral apparatus may assist in the maintenance of a favorable left ventricular geometry in order to favorably affect postoperative ventricular function.

Mitral valve repair is favored in almost all cases when feasible because a prosthesis and its attendant potential problems are avoided. Therefore, the issue of anticoagulation can be avoided, as well as the potential for future prosthetic failure. Furthermore, mitral repair preserves the entire mitral apparatus, which is associated with superior postoperative survival and left ventricular function.[107] The reoperation rates for mitral valve replacement and repair appear to be similar with a reoperation rate approaching 10% by 10 years for those undergoing repair.[110,111]

The feasibility of repair versus replacement can be assessed echocardiographically, either with transthoracic or transesophageal methods.[106] Repair is usually feasible when limited calcification of the leaflets or annulus is present, limited prolapse of only one leaflet exists, or when pure annular dilatation or valvular perforation is present. On the other hand, replacement may be required if extensive calcification, severe prolapse, infection, or subvalvular involvement is seen.[112,113]

Symptomatic Patients

Symptomatic patients with severe chronic mitral insufficiency should be considered candidates for surgical intervention.[114] Patients with normal left ventricular function and little or no chamber enlargement can be candidates for surgery even if only mild symptoms are present, particularly if mitral valve repair is feasible.[115] Mitral valve surgery is also recommended when mild-to-moderate left ventricular dysfunction is present (EF 30% to 55%) or when end-systolic dimension exceeds 45 mm.[116] Suboptimal outcome is more likely when severe left ventricular dysfunction is present (EF < 30% or end-systolic dimension > 55 mm).[117] Still, surgery is reasonable, particularly if repair is feasible, whether a primary leaflet abnormality is present or functional insufficiency is present.[91]

Asymptomatic Patients

Despite the absence of symptoms, patients with chronic severe mitral regurgitation and echocardiographic indicators of left ventricular dysfunction are candidates for mitral valve surgery.[118] Indicators of ventricular dysfunction include a reduction in EF less than 55% to 60% and an end-systolic dimension exceeding 45 mm.[94,118] Although mitral valve repair is preferred, a survival advantage can be expected whether repair or replacement is performed.[115,119]

Some lack of agreement exists regarding surgical intervention in those without indicators of left ventricular dysfunction (EF > 60% or ESD < 40 mm). However, when atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise) is present, early surgery is considered, especially if repair is feasible.[41,120] This recommendation is supported by evidence suggesting that atrial fibrillation independently predicts cardiac death and that a concomitant surgical Maze procedure may prevent future events with the restoration of normal sinus rhythm.[121-123] In the absence of these factors, asymptomatic patients with normal left ventricular function should be followed closely with noninvasive studies. Subsequently, prospective studies suggested that asymptomatic patients with effective regurgitant orifice areas exceeding 0.4 cm^2 have a more favorable outcome with mitral valve surgery despite the absence of indicators for left ventricular dysfunction because increasing EROA has implications for decreased survival with medical management.[105] Although these data are interesting, use of a single measurement to base referral for surgery is not advocated.

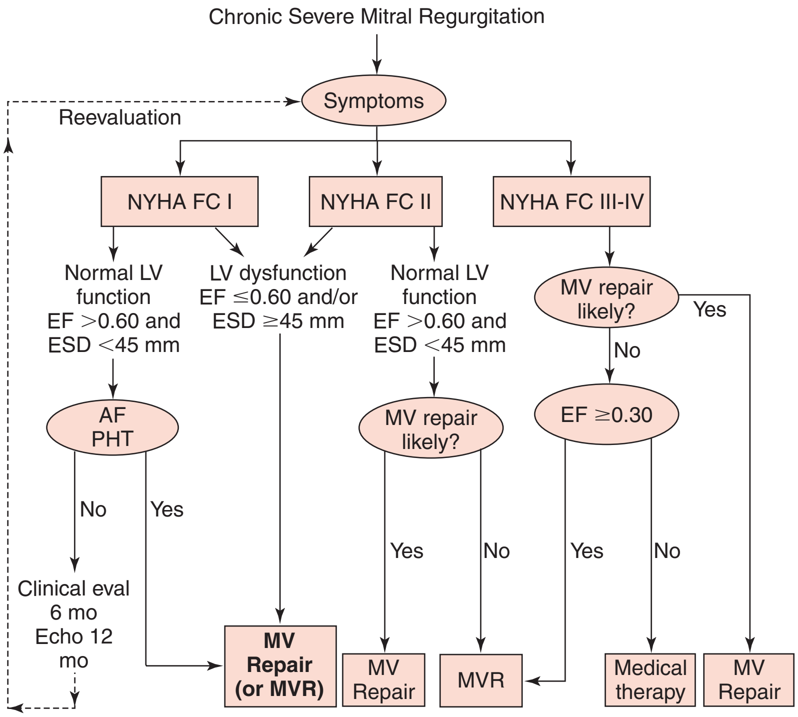

Figure 46–6 Management strategy and timing of surgery in patients with mitral regurgitation. (Redrawn from ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee on Management of Patients with Valvular Heart Disease]. J Am Coll Cardiol 1998;32: 1486-588.)

Overall Approach

The decision for surgery is based largely on the presence or absence of symptoms and size and function of the left ventricle. If surgery is performed, valve repair is preferred over replacement, and if replacement is performed, chordal preservation is always preferred. Patients with echocardiographic indicators of left ventricular dysfunction are candidates for surgery irrespective of symptomatology. When severe left ventricular dysfunction is present, mitral valve surgery is reasonable when repair is feasible but can be problematic when valve replacement is attempted. When atrial fibrillation or pulmonary hypertension is present in asymptomatic individuals, early surgery should be considered, especially when repair is likely. Otherwise, close monitoring is usually advocated with noninvasive measures (Fig. 46–6).

RIGHT-SIDED VALVE DISEASE

Tricuspid Valve Disease

In adults, severe tricuspid insufficiency can result from a host of primary leaflet abnormalities or secondary dysfunction. Primary leaflet abnormalities include bacterial endocarditis, carcinoid disease, and trauma. Tricuspid insufficiency may also result from right ventricular failure or from annular dilatation.[124] A dense, triangular, early-peaking tricuspid regurgitant envelope seen on spectral Doppler, systolic reversal of hepatic vein flow, and a large vena contracta width (>0.7 cm) are echocardiographic indicators of severe tricuspid insufficiency.[81,125]

Severe tricuspid insufficiency may be a marker for poor outcomes when present in combination with other valve disease.[126] When right ventricular failure and tricuspid insufficiency result from reversible left-sided cardiac disease, particularly mitral stenosis, an improvement in tricuspid insufficiency may result with surgical correction of the mitral stenosis. However, balloon valvuloplasty for mitral stenosis alone may not completely resolve tricuspid insufficiency.[127] Therefore, tricuspid annuloplasty at the time of surgical correction for mitral stenosis may be appropriate.[128]

Timing of surgical intervention in severe isolated tricuspid insufficiency is controversial. However, when symptoms are refractory to medical therapy, surgical intervention is reasonable. When surgical intervention is contemplated, tricuspid annuloplasty is usually performed. However, when the leaflets are abnormal or severely diseased, valve replacement may be necessary.

Significant tricuspid stenosis is a relatively rare entity but when present is usually the result of rheumatic involvement. Both stenosis and regurgitation may be present. The clinical status of the patient usually determines the treatment strategy. Although balloon valvuloplasty has been attempted,[129] significant TR may result. Therefore, bioprosthetic valve replacement is often necessary.[130,131]

Pulmonary Valve Disease

Acquired pulmonic valve disease in adults is rare, with the vast majority of lesions originating from congenital malformation of the valve itself. Pulmonic stenosis in adolescents and young adults is often approached percutaneously and is often performed when peak transpulmonic gradients exceed 30 mm Hg at catheterization in symptomatic patients.[132] Significant pulmonic insufficiency can result following surgical repair of tetralogy of Fallot.[133] The timing of pulmonary valve replacement with a bioprosthesis is controversial but optimally should be performed before irreversible right ventricular dysfunction.[134,135]

FUTURE DIRECTIONS

Although surgical correction for valvular heart disease has been largely based on the presence of symptoms and results of noninvasive imaging, increasing clinical data suggest a role for the measurement of circulating biomarkers. Natriuretic peptides have not only been shown to help in the diagnosis of heart failure[136] but also to be independent predictors of outcome.[137] In valvular disease, natriuretic peptides may be a reflection of left ventricular wall stress.[138] Clinically, plasma levels of B-type natriuretic peptide (BNP) have been shown to parallel the severity of valvular disease and NYHA class among patients with aortic stenosis and mitral insufficiency.[139,140] Further clinical data suggest that BNP measurement may be helpful in discerning symptom onset[141] or clinical deterioration[142] in aortic stenosis and appear to predict symptom-free survival and postoperative outcome among such patients.[143] Although clinical data are still emerging, measurement of natriuretic peptides may soon complement our current strategies in timing surgical intervention in valvular heart disease.

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Chapter 47

Surgery for Valvular Heart Disease

Lishan Aklog and Anelechi Anyanwu

CHAPTER CONTENTS

INTRODUCTION

Although medical therapy can ameliorate symptoms and, in some instances, slow the progression of early-stage valvular heart disease, surgical intervention has been, and remains, the primary and only definitive therapy for nearly all patients with advanced valvular heart disease.

Before the introduction of closed mitral commissurotomy by Elliot Cutler at the Peter Bent Brigham Hospital in 1923, the natural history of most forms of valvular heart disease was progressive cardiopulmonary dysfunction and death. Although his subsequent results were poor, he showed for the first time that surgical manipulation of the diseased valve could correct the physiologic dysfunction, alleviate symptoms, and alter the natural history of disease. Twenty-five years later his successor Dwight Harken, Charles Bailey, and others perfected the technique and demonstrated that surgical correction of valvular heart disease could be routine and durable.

Not until the clinical introduction of the heart-lung machine (John Gibbons, 1953) and the successful deployment of valvular prostheses, first in the descending aorta (Charles Hufnagel, 1952) and then intracardiac (Nina Braunwald, 1960), could the full spectrum of valvular lesions be approached surgically.[1,2] The modern era of valvular heart surgery began soon after with the introduction of the first widely used and highly successful prosthesis, the Starr-Edwards caged-ball mechanical valve (Albert Starr, 1961).[3]

Other milestones in surgical therapy for valvular heart disease (Table 47–1) include the introduction of xenograft bioprostheses, valved-conduit replacement of the aortic root, the development of reproducible techniques for mitral valve repair by Alain Carpentier,[4,5] and the introduction of minimally invasive techniques in the late 1990s.

Currently, the vast majority of patients with advanced valvular heart disease can be offered surgical therapy with very good short- and long-term results including those with severe ventricular dysfunction, advanced age, significant pulmonary hypertension, and other comorbidities. Operative mortality rates have declined despite a higher-risk patient profile, presumably as a result of refined surgical techniques and technologies, improved myocardial protection, and advances in perioperative care. Recent advances in less-invasive surgical approaches and accelerated postoperative care plans have decreased hospital stays and recovery times. Finally, refined repair techniques and improved prostheses have improved longer-term outcomes including reoperation rates and thromboembolic complications.

GENERAL CONSIDERATIONS

Epidemiology

Approximately 100,000 patients in the United States undergo valvular heart surgery each year. The overall volume of valvular surgery appears to be growing (Fig. 47–1A). As expanding percutaneous interventions erode into isolated coronary surgery volume, most centers are reporting an increasing share of valvular surgery (see Fig. 47–1B). The most commonly performed procedure is aortic valve replacement with or without concomitant coronary bypass grafting (see Fig. 47–1C). Mitral valve repair, although still underused,[6] is growing steadily. There has also been a greater appreciation of the importance of correcting tricuspid regurgitation, usually concomitant with mitral valve surgery. Pulmonic valve surgery is quite rare in adults and is usually performed in the context of long-standing congenital heart disease or carcinoid heart disease. Pulmonic valve surgery is not discussed in this chapter.

Indications

The specific indications for surgical intervention vary from valve to valve and are discussed separately. Generally, however, the indications can be primary or secondary. Traditionally, the primary indication for surgery has been the onset of symptoms, most notably symptoms of left or right heart failure, or both, but also angina, syncope, and arrhythmias. With wider utilization of echocardiography and improved surgical outcomes, echocardiographic evidence of ventricular strain (dilatation or dysfunction, or both) has become the primary indication for surgery in an increasing number of asymptomatic or mildly symptomatic patients. Most recently, the primary indications for mitral valve repair have been broadened to include some asymptomatic patients with normal ventricular function and dimensions.[7]

Many patients without a primary indication for intervention on a particular valve will undergo valve surgery at the time of another cardiac surgery procedure, such as coronary bypass surgery, other valve surgery, or aortic surgery. The

Table 47–1 Historical Highlights

1914	Tuffier	Closed aortic valvulotomy (digital)
1923	Culter	Closed mitral valvulotomy (valvulotome)
1925	Soutter	Closed mitral valvulotomy (digital)
1948	Harken, Bailey	Closed mitral valvulotomy (digital), first large series
1952	Hufnagel	Descending thoracic aortic prosthesis (caged ball), first AR surgery
1953	Gibbons	Heart-lung machine
1956	Murrary	Descending thoracic aortic prosthesis (homograft)
1956	Lillehai	Open mitral commissurotomy
1956	Lillehai	Open mitral annuloplasty, first MR surgery
1960	Braunwald	Mechanical prosthetic MVR (polyurethane)
1960	Harken	Mechanical prosthetic AVR (caged ball)
1961	Starr	Mechanical prosthetic MVR with long-term survival (caged ball)
1962	Ross, Barrett-Boyes	Homograft AVR (orthotopic)
1965	Carpentier	Xenograft prosthetic AVR (porcine)
1967	Ross	Autograft AVR
1968	Carpentier	Prosthetic annuloplasty ring
1968	Bentall	Aortic root replacement (valved conduit)
1970s	Carpentier	Functional approach to mitral valve repair
1983	Yacoub	Valve sparing aortic root replacement (remodeling)
1992	David	Valve sparing aortic root replacement (inclusion)
1996	Cosgrove, Gundry	Minimally invasive aortic and mitral valve surgery (direct access)
1996	Carpentier, Chitwood	Minimally invasive mitral valve surgery (video assisted)
1998	Carpentier	Minimally invasive mitral valve surgery (robotic)

AVR, aortic valve replacement; MVR, mitral valve replacement.

threshold for intervention as a concomitant procedure is usually lower than as a primary procedure, and valve repair or replacement may be indicated for moderate or even mild degrees of stenosis or regurgitation. The decision to intervene is based on an understanding of the natural history of these valvular lesions and is primarily aimed at preventing subsequent progression of heart failure symptoms or the need for late reoperation.

Preoperative Evaluation and Optimization

Patients undergoing valvular surgery require thorough preoperative evaluation and optimization to assure the best possible outcomes.

History and Physical

A detailed history and physical examination is fundamental. In addition to carefully characterizing the symptom profile of the valve disease, it is important to determine if there is a history of palpitations or known arrhythmia; risk factors for or known coronary artery disease; stroke or transient ischemic attacks (TIAs); lung, liver, or renal disease; GI bleeding; peripheral vascular disease; bleeding or hypercoagulable conditions; and recent infections. In addition to careful cardiopulmonary auscultation, key elements of the physical examination include a good dental examination, assessment of jugular venous pressures, carotid bruits and peripheral pulses, hepatomegaly, and availability of venous or arterial conduits for possible concomitant bypass grafting.

Documenting the baseline rhythm, any bundle branch blocks, and baseline ST and T-wave changes is important for intraoperative and postoperative management. In addition to identifying unsuspected cardiopulmonary pathology, the chest x-ray provides a plethora of useful preoperative information including chest wall anatomic details (useful for planning less-invasive surgical incisions) and the presence of pathologic calcification (aorta, valves, annuli). Each of these elements can have a significant impact on surgical decision-making, timing, and choice of prosthesis.

Echocardiography

Nearly all patients referred for surgery will have undergone a transthoracic echocardiogram to make the diagnosis, and this will often be supplemented by a transesophageal study. Careful characterization of the primary valve lesion is important and can be invaluable for surgical planning and counseling the patient on the likely intraoperative events. In addition to measuring the degree of stenosis or regurgitation, or both, the specific etiology can often be determined. The use of quantitative methods for measuring mitral regurgitation (PISA, ERO, and RV) should be encouraged. The other valves should be carefully interrogated to rule out multivalve disease. Estimation of biventricular function is obviously critical, but so are ventricular dimensions, hypertrophy, any ventricular outflow tract obstruction and TR-jet derived estimates of pulmonary artery pressure. Other important findings include atrial dilatation, thrombus, patent foramen ovale, and occasional rare anomalies such as a persistent left-sided superior vena cava (SVC). In young patients in whom coronary arteri-

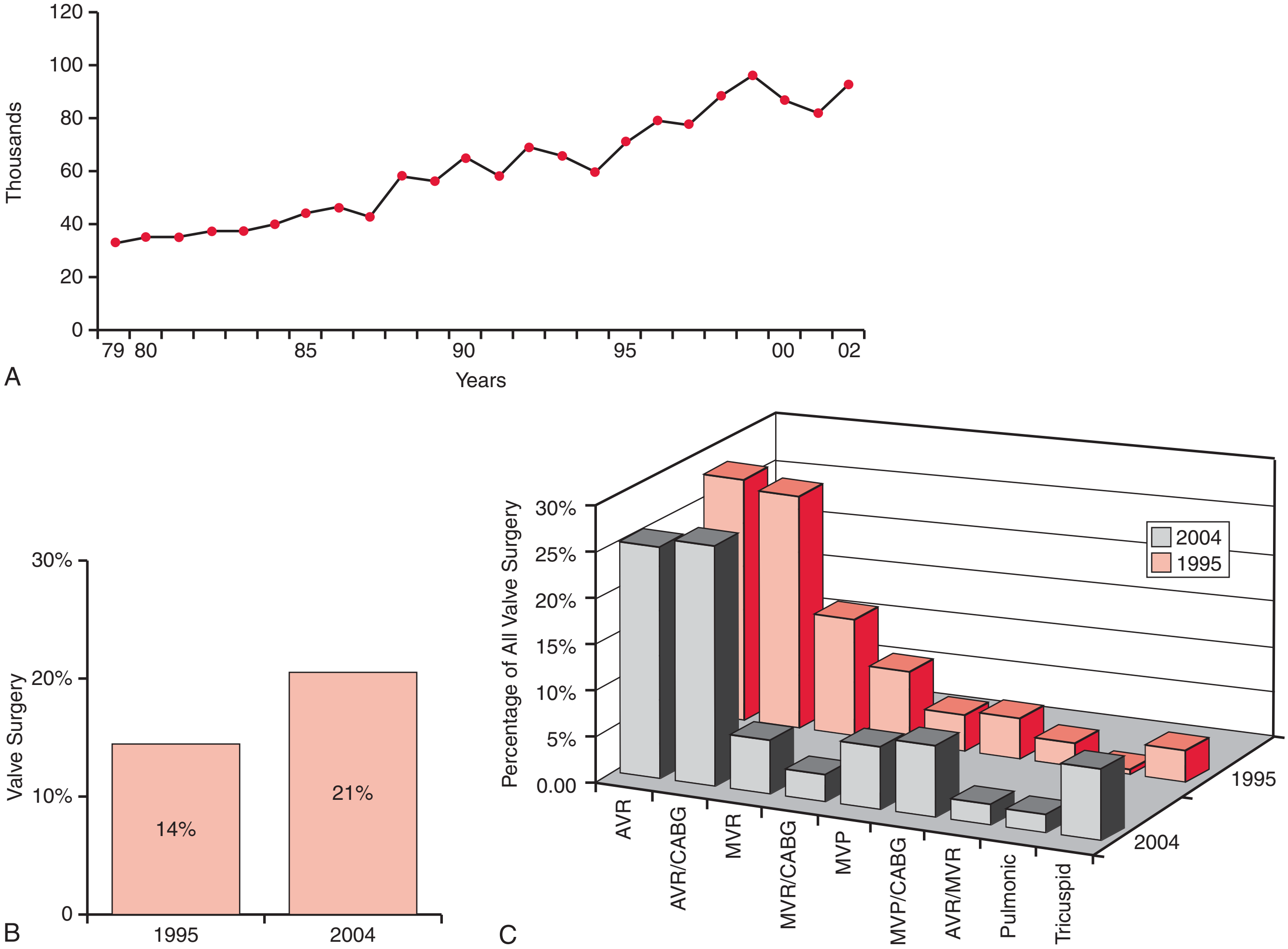


Figure 47–1 Valve surgery statistics. **A,** Overall number of valve operations per year in the United States 1979-2003 (National Center for Health Statistics). **B,** Valve operations as a percentage of all cardiac operations in 1995 versus 2004 (Society of Thoracic Surgery Database 2005 Executive Summary, *www.sts.org*). **C,** Specific valve operations as a percentage of all valve operations in 1995 versus 2004 (Society of Thoracic Surgery Database 2005 Executive Summary, *www.sts.org*).

ography may be deferred, echocardiographic identification of the coronary ostia may be important.

Even if the primary valve lesion was well characterized on a series of older echocardiograms, it is advisable to repeat the study within a month or so of surgery to reassess ventricular and other valvular function, which can sometimes progress rather rapidly. In some patients in whom the decision to proceed with surgery is equivocal (e.g., low-gradient aortic stenosis [AS] with poor left ventricular [LV] function), stress echocardiography may provide useful information.

Cardiac Catheterization

In the majority of patients about to undergo valvular surgery, the complete hemodynamic picture can be obtained with echocardiography alone. Occasionally, however, right or left heart catheterization, or both, may be indicated to more precisely delineate the hemodynamic picture, especially stenotic gradients and the severity of pulmonary hypertension. Angiographic assessment of valvular regurgitation does not add much to the echocardiogram and can frequently underestimate eccentric jets.

As echocardiography has improved, the primary indication for preoperative catheterization is now coronary angiography, which is indicated in patients with known CAD or significant CAD risk factors. The age threshold for coronary angiography in patients without risk factors is usually 40 years for men and 50 years for women, although some would recommend routine coronary angiography in men as young as 35 years. The likelihood of CAD in preoperative valve patients varies from about 1% in degenerative mitral valve disease to more than 50% in calcific AS.

The specific question of whether a stenotic aortic valve should be crossed to confirm hemodynamics is controversial. Most surgeons are comfortable proceeding on the basis of a good echocardiogram with catheter-based hemodynamic assessment only in equivocal cases. A contemporary study highlighted the real risk of embolism during attempts to cross a stenotic valve and encouraged a selective approach.[8]

Other Preoperative Testing

Although echocardiography remains the mainstay of preoperative testing, cardiac magnetic resonance imaging provides

excellent outstanding anatomic and physiologic data in patients with valve disease. The specific indications for its use in this setting, however, have not been established. Other imaging may be indicated in specific clinical scenarios. A head CT scan may be useful in patients with prior CVA or to rule out mycotic aneurysms in patients with endocarditis. Preoperative carotid ultrasound is frequently performed if carotid stenoses are suspected. A chest CT scan may be useful to more precisely determine the relationship between the heart and chest wall structures to plan minimally invasive incisions.

Holter monitoring may be useful in patients with suspected atrial arrhythmia to determine whether concomitant arrhythmia surgery should be considered. If indicated, formal electrophysiologic testing for ventricular arrhythmias is typically performed postoperatively because the substrate may be altered by surgical intervention.

In patients with dyspnea as a primary symptom, it may be difficult to determine the relative cardiac and pulmonary contributions to their symptoms and the degree to which correcting the cardiac lesion will improve their symptoms. Pulmonary function tests can help clarify this and allow the physician to provide the patient with realistic expectations from surgery.

Medical Therapy

Whether a patient presents for urgent aortic valve replacement for acute AR secondary to endocarditis or for purely elective mitral valve repair, the potential for preoperative medical optimization should be considered. Such efforts, however minor they might appear, may significantly assist intraoperative care and improve postoperative outcomes, especially in high-risk patients. Even in the most urgent settings, such as a patient in shock with acute MR from papillary muscle rupture, the time until the operating room is ready can be used to stabilize the hemodynamics with inotropic agents and an intraaortic balloon pump if not contraindicated.

In less urgent settings every effort should be made to optimize the patient for surgery, remaining careful not to miss the opportunity to intervene by trying to make the patient "perfect." Patients with decompensated heart failure may benefit from aggressive outpatient or inpatient diuresis and titration of other cardiac medications. Elderly or debilitated patients may benefit from preoperative physical therapy or nutritional support. Efforts to improve rate control or even cardioversion may be indicated in patients with supraventricular arrhythmias including atrial fibrillation. Smoking cessation programs or formal pulmonary rehabilitation may be helpful. Patients on hemodialysis are often admitted a few days preoperatively for more aggressive dialysis runs. Patients on warfarin should stop at least 4 to 5 days before surgery, and those with strong indications for anticoagulation are usually admitted for IV heparin or treated as an outpatient with low-molecular-weight heparin. On the other hand, the current practice is to continue aspirin for patients with coronary disease through surgery.

Preoperative optimization of high-risk patients undergoing mitral valve surgery may be particularly important, especially those with significant pulmonary hypertension and ventricular dysfunction. Our group recently reported on a preoperative regimen including nesiritide, which decreased PA pressures and operative mortality relative to predicted in high-risk mitral valve surgery patients (0% versus 23%).[8a]

Surgical Approaches

Median Sternotomy

The median sternotomy remains the primary approach for most patients undergoing valve surgery. Median sternotomy is the only viable approach for those undergoing concomitant bypass grafting. It provides direct access to all important cardiovascular structures, and valve exposure is usually excellent. A full sternotomy can be performed through a fairly limited skin incision (12 to 18 cm) in patients with a favorable body habitus who desire a better cosmetic result. After pericardiotomy, the heart and great vessels are inspected and, increasingly, the ascending aorta is scanned to rule out significant plaque or atheroma, which might alter cannulation or aortic clamping techniques.

Minimally Invasive Approaches

Over the past decade surgeons have explored alternative incisions for accessing heart valves that aim to reduce surgical invasiveness and also yield a more cosmetic result. The primary incisions (Fig. 47–2) are typically 5 to 10 cm and include mini-thoracotomies (anterior, lateral, and axillary) and partial sternotomies (upper, lower). The approaches can be categorized as direct access, videoscopic, or robotic assisted. With *direct access* approaches, surgical manipulation is performed under direct vision through the primary incision. Cannulation for cardiopulmonary bypass can be performed centrally through this incision or peripherally. *Videoscopic* mitral valve surgery is performed through a small working incision and one or more additional endoscopic ports. Cannulation for cardiopulmonary bypass is usually performed peripherally. The valve is viewed on a monitor, and the tissues are manipulated using specialized endoscopic instruments. *Robotic* mitral valve surgery is similar, but the imaging and instruments are integrated into a robotic surgical device (da Vinci, Intuitive Surgical) which is manipulated remotely from a separate console. Some surgeons have used this technology to perform truly endoscopic mitral valve surgery.

The major advantage of minimal access approaches is cosmetic. Other potential advantages include less pain (because of less tissue retraction) and less bleeding (because of less dissection). All minimal access approaches leave at least part of the sternum intact, thereby preserving chest wall integrity (and possibly resulting in less wound dehiscence and less respiratory morbidity). Minimally invasive approaches are more technically demanding, require more surgical skill, and pose unique surgical challenges (e.g., reduced tactile feedback, modification of cannulation techniques, difficulties in myocardial protection, and de-airing). There is a learning curve to the procedure, and the procedures generally take longer to perform. With adequate training and experience, minimally invasive valve surgery can be undertaken with comparable or superior results to conventional technique.

Minimally invasive aortic valve replacement through a partial upper sternotomy is now widely practiced and has become the standard approach for isolated aortic valve replacement at many centers. Although published data support the safety and efficacy of this approach, they are mixed on whether real clinical advantages beyond cosmesis exist.[9-14] Videoscopic and robotic mitral valve surgery is being performed mostly at

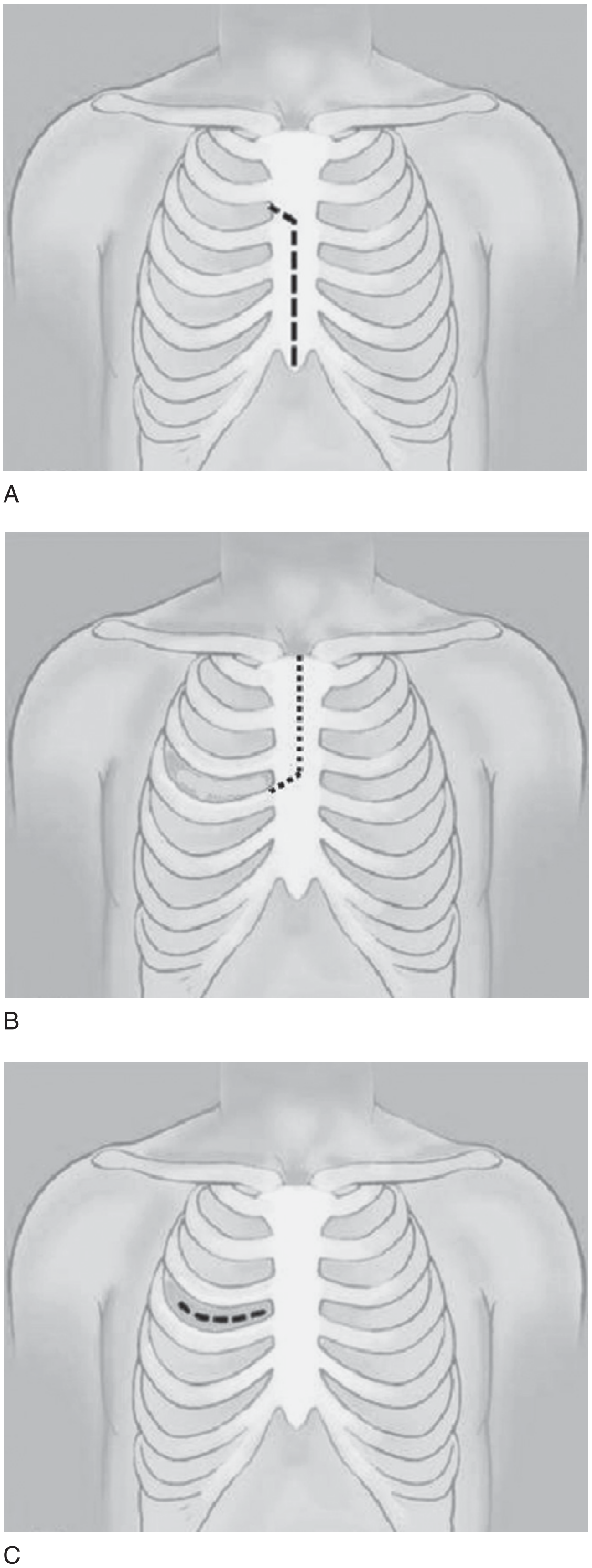


Figure 47–2 (*See also Color Plate 47–2.*) Minimally invasive valve surgery incisions. **A,** Lower partial sternotomy. **B,** Upper partial sternotomy. **C,** Right mini-thoracotomy.

specialized centers. Again, published data support its safety and efficacy but have not shown it to be superior with regard to hard clinical endpoints.[14a,14b]

Prostheses

Currently available valve prostheses are the product of nearly half a century of engineering, biochemical, and clinical research and are designed to provide maximum hemodynamic performance, durability, and freedom from complications. Nonetheless, the "holy grail" of the perfect valve prosthesis—with no obstruction to flow, no regurgitation, lifelong durability, and no significant complications—may never be reached. In fact, patients and physicians will likely always be faced with the need to balance the pros and cons of each prosthesis. The currently available FDA-approved prostheses and the relative advantages and disadvantages of each class of prostheses are noted in Tables 47–2 and 47–3. The most commonly used valves are shown in Figure 47–3. The annuloplasty devices are described later with mitral valve repair.

The primary differentiating characteristics of valve prostheses are their hemodynamic profile and the incidence of valve-related complications. A consensus panel of the Society of Thoracic Surgery (STS) and the American Association of Thoracic Surgery (AATS) published standard definitions and guidelines for reporting valve-related complications in 1996.[2] The panel defined six specific, nonfatal valve-related events—structural valve degeneration, nonstructural valve degeneration, valve thrombosis, embolism, bleeding, and operated valvular endocarditis (Table 47–4). Time-related complications are typically reported as linearized rates (thrombosis, embolism, bleeding) or using actuarial methods (structural valve degeneration, endocarditis). As more elderly patients underwent valve surgery, it became apparent that actuarial methods can overestimate these rates because they do not censor patients who die from other causes. Reporting actual survival on the basis of Grunkemeier's cumulative incidence method[15,16] has become more popular because it is more relevant to clinical decision-making.

Mechanical Valves

Mechanical valves are generally characterized by good hemodynamics, excellent durability, and ease of implantation. These benefits must be balanced against a lifelong need for moderate anti-coagulation and sometimes troubling valve noise. Their dominant position has been steadily eroded over the past decade by improved bioprostheses and increasing mitral valve repair.

Mechanical valves are of three types—caged ball, tilting disc, and bileaflet. The Starr-Edwards valve, which consists of a Silastic ball within a titanium cage, has remained on the market, essentially unchanged, for nearly 4 decades. Despite a remarkable history and excellent durability, it is rarely used because it has been surpassed by valves with superior thromboembolic and hemodynamic profiles. In a tilting disc valve, such as the Medtronic-Hall valve (1977), the ball is replaced by a flat disc that tilts open along retaining guides during systole, increasing central flow and improving hemodynamics and thromboresistance. The St. Jude mechanical valve, also introduced in 1977, was the first bileaflet valve and, with more

Table 47–2 FDA-approved and U.S.-marketed Heart Valve Prostheses

Type/Name				Manufacturer	Approval Year	Size Range Aortic (mm)	Size Range Mitral (mm)	Models
Mechanical Valves	*Caged Ball*		Starr-Edwards	Edwards Lifesciences	1966	21-31		
	Tilting Disc		Medtronic-Hall	Medtronic	1977	20-31	23-33	
	Bileaflet		St. Jude Medical	St. Jude Medical	1977	17-31	17-33	Standard, Masters HP, Regent
			Carbomedics	Sulzer Carbomedics	1993	16-31	16-33	Standard, Reduced, Optiform, TopHat
			On-X	Medical Carbon Research Institute	2001	19-29	23-33	Standard, Conform-X
			ATS Medical Open Pivot	ATS Medical	2000	16-31	16-33	Standard, AP
Biological Valves	*Stented Porcine*		Carpentier-Edwards	Edwards Lifesciences	1975	19-31	25-35	Standard, SAV, Duraflex
			Hancock	Medtronic	1969	21-29	25-33	Standard, II, MO II
			Mosaic	Medtronic	2000	19-29	25-33	
			SJM Biocor	St. Jude Medical	2005	19-29	25-33	Standard, Supra
	Stented Bovine Pericardial		Carpentier-Edwards Perimount	Edwards Lifesciences	1991 (A) 2000 (M)	19-29	25-33	Standard, RSR, Magna
	Stentless Porcine		Freestyle	Medtronic	1997	19-29	N/A	
			Prima Plus	Edwards Lifesciences	2001	21-29	N/A	
			Toronto SPV	St. Jude Medical	1997	21-29	N/A	
	Aortic Homograft			Cryolife, Lifenet	N/A	Varies	Varies	

Table 47–2 FDA-approved and U.S.-marketed Heart Valve Prostheses—cont'd

Type/Name				Manufacturer	Approval Year	Size Range Aortic (mm)	Size Range Mitral (mm)	Models
Annuloplasty Devices	Complete	Rigid/Semirigid	Carpentier-Edwards Classic	Edwards Lifesciences	1968	26-40	26-40	Different mitral and tricuspid models
			Carpentier-Edwards Physio	Edwards Lifesciences	1993	24-40		
			Carbomedics AnnuloFlo	Sulzer Carbomedics	1997	26-30		
			SJM Seguin	St. Jude Medical	1997	24-40		
			Edwards MC3	Edwards Lifesciences	2002		26-36	Tricuspid only
			Carpentier-McCarthy-Adams IMR ETlogix	Edwards Lifesciences	2003	24-34		
			Geoform	Edwards Lifesciences	2003	26-32		
		Flexible	Duran	Medtronic	1989	25-35	*	
			Carbomedics AnnuloFlex	Sulzer Carbomedics	1999	26-30		
			SJM Tailor	St. Jude Medical	2000	25-35		
	Partial	Rigid/Semirigid	Colvin-Galloway Future	Medtronic	2001	26-38		
		Flexible	Cosgrove-Edwards	Edwards Lifesciences	1993	26-38	*	
			Duran	Medtronic	1989	25-35		Complete ring can be converted to partial band by excising anterior segment
			Carbomedics AnnuloFlex	Sulzer Carbomedics	1999	26-30		
			SJM Tailor	St. Jude Medical	2000	25-35		

*All flexible rings and partial bands can be used in the tricuspid position.

than 1 million implants, remains the world's most popular valve prosthesis. It is manufactured from pyrolytic carbon with each leaflet rotating over a fixed range within pivots in the inner surface of the ring. Several other companies market similar pyrolytic carbon bileaflet valves that purport advantages on the basis of the purity of the carbon (On-X), pivot designs (ATS Medical) and supra-annular location of the leaflets and pivots (Carbomedics).

Numerous long-term studies have evaluated the absolute and relative performance of currently available mechanical valves. Several primary findings have been made. The incidence of structural valve degeneration of the currently marketed

Table 47–3 Valve Prostheses Characteristics

	Mechanical	Stented Xenograft	Stentless Xenograft	Homograft	Autograft
Need for anticoagulation	+	++	+++	+++	+++
Freedom from thromboembolism	+	++	?+++	+++	+++
Durability	+++	++	?++	++	+++
Ease of operation	+++	+++	++	++	+
Hemodynamic performance	++	+	+++	+++	+++
Resistance to infection	+	+	?++	+++	+++
Noise	++	+++	+++	+++	+++

Note: In the scale used for this table the greater the number of + signs the greater the relative advantage of a particular valve type.

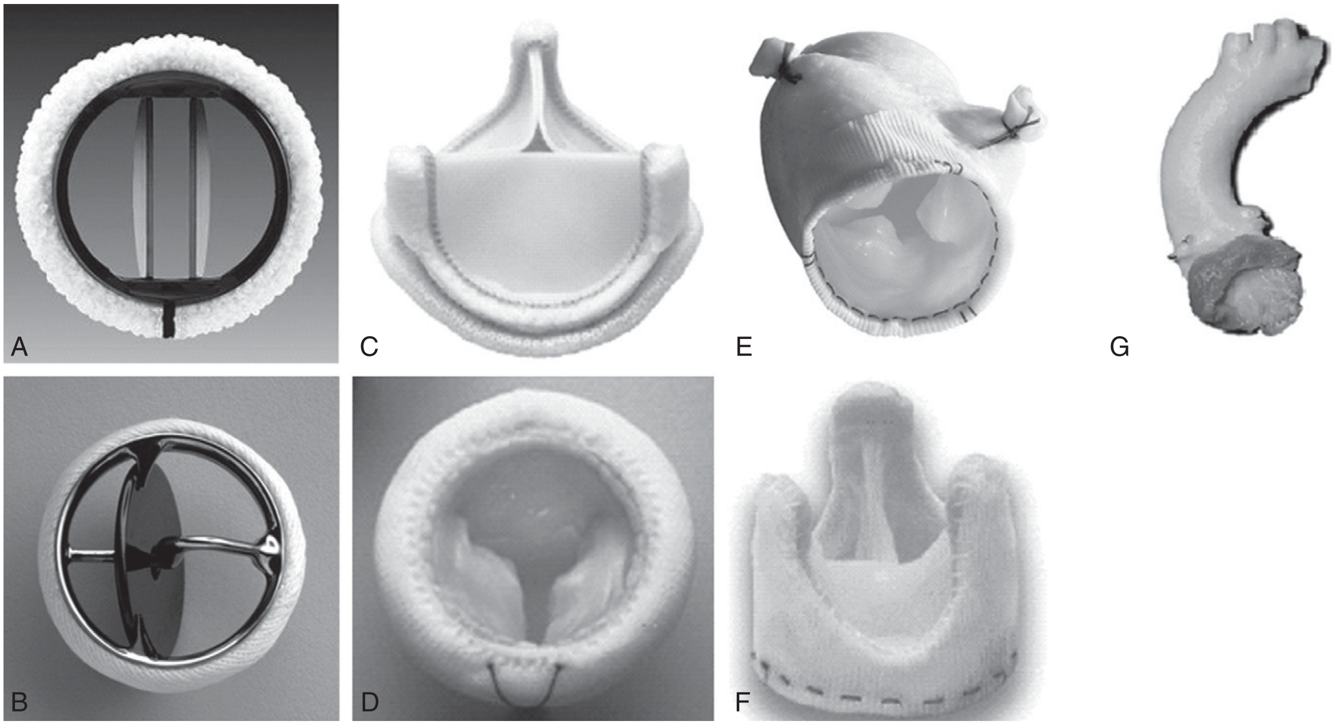


Figure 47–3 (*See also Color Plate 47–3.*) Valve prostheses. **A,** St. Jude Medical bileaflet mechanical valve. **B,** Medtronic-Hall tilting disc mechanical valve. **C,** Carpentier-Edwards Magna stented bovine pericardial aortic bioprosthesis. **D,** Medtronic Mosaic stented porcine mitral bioprosthesis. **E,** Medtronic Freestyle stentless porcine full root bioprosthesis. **F,** St. Jude Medical Toronto-SPV stentless porcine subcoronary bioprosthesis. **G,** Aortic homograft.

mechanical valves is vanishingly low. The annual linearized rates (events/patient-year) of thromboembolism (0.5% to 4%), thrombosis (0% to 0.5%), and major bleeding complications (0.5% to 4%) vary widely from study to study and are greater for valves in the mitral than in the aortic position. A low but finite incidence of reoperation (5% to 10% at 15 to 20 years) exists for endocarditis, thrombosis, or nonstructural dysfunction (e.g., pannus overgrowth, endocarditis, perivalvular leak).

Grunkemeier et al[17] performed a meta-analysis of complication rates from the two most popular mechanical valves, St. Jude and Carbomedics, and found similar rates of thromboembolism (1.6% aortic, 2% to 2.5% mitral) and bleeding (1.5% aortic, 1.3% to 1.4% mitral). The Carbomedics valve had a lower thrombosis rate in the aortic position (0.02% versus 0.15%) but higher in the mitral position (0.17% versus 0.33%) (Table 47–5, Fig. 47–4). Several retrospective studies have suggested slightly higher long-term complication rates with the Medtronic-Hall valve compared with the bileaflet valves,[18,19] although a small randomized trial could not detect a difference.[20] The data on the newer valves (ON-X, ATS) are also comparable, but so far no irrefutable data support that they are superior.

The recommended target INR for the bileaflet and Medtronic-Hall valves is 2.0 to 3.0 in the aortic position and 2.5 to 3.5 in the mitral. Higher levels and the addition of aspirin should be considered in patients who are at higher risk for thromboembolism (atrial fibrillation, prior thromboembolism, hypercoagulable state). Significant interest has been expressed in alternatives to warfarin anticoagulation including the new oral direct thrombin inhibitor ximelagatran and even dual antiplatelet therapy with aspirin/clopidogrel in aortic valves. Data to determine whether these will be safe and effective alternatives are inadequate to date.

Table 47–4 Definition of Valve-related Complications

Structural valvular deterioration	Any change in function of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation exclusive of infection or thrombosis, such as wear, calcification, or leaflet tear.
Nonstructural dysfunction	Any abnormality resulting in stenosis or regurgitation at the operated valve that is not intrinsic to the valve itself, exclusive of thrombosis and infection, such as pannus overgrowth, paravalvular leak, inappropriate sizing or positioning; residual leak or obstruction; and clinically important hemolytic anemia.
Valve thrombosis	Any thrombus, in the absence of infection, attached to or near an operated valve that occludes part of the blood flow path or that interferes with valvular function.
Embolism	Any embolic event that occurs in the absence of infection after the immediate perioperative period. A neurologic event includes any new, temporary, or permanent focal or global neurologic deficit. A peripheral embolic event produces symptoms from complete or partial obstruction of a peripheral artery. Immediate postoperative neurologic deficits and myocardial infarction are generally excluded.
Bleeding event	Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury or requires transfusion, whether or not anticoagulants or antiplatelet drugs are being taken.
Operated valvular endocarditis	Any infection involving an operated valve, based on customary clinical criteria. Morbidity associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak, is included under this category and is not included in other categories of morbidity.

Table 47–5 Pooled Event Rates and Hazard Ratios (HR) for Comparison of Event Rates

		Pooled event rates		Valve only in model	
Event	Valve	Rate (%/y)	Cochran* *P* Value	HR	95% CI
Aortic position					
Thromboembolism	St. Jude	1.58	<.001	1.06	0.68-1.66
	Carbomedics	1.59	<.001		
Valve thrombosis	St. Jude	0.14	0.005	0.16	0.05-0.56
	Carbomedics	0.02	0.777		
Bleeding	St. Jude	1.32	<.001	1.06	0.66-1.70
	Carbomedics	1.45	<.001		
Mitral position					
Thromboembolism	St. Jude	2.45	<.001	0.72	0.38-1.38
	Carbomedics	1.95	<.001		
Valve thrombosis	St. Jude	0.17	0.111	1.94	0.98-3.84
	Carbomedics	0.33	0.03		
Bleeding	St. Jude	1.26	<.001	1.1	0.60-2.00
	Carbomedics	1.41	<.001		

Stented Xenografts

The first xenograft bioprostheses were developed by Carpentier and Hancock in 1969. They consisted of a rigid or semirigid cloth-covered stent to which porcine aortic valve cusps were attached. Cusps created from bovine pericardium were later applied to similar stent structures. The key development was the introduction of glutaraldehyde fixation. By cross-linking collagen fibers and eliminating viable cells, this treatment increases the durability of the xenograft tissue and decreases its antigenicity. It soon became clear, however, that the Achilles heel of glutaraldehyde fixation was subsequent calcification, which is the final common pathway for structural valve degeneration of most bioprostheses. In addition to the loss of cusp mobility, areas of calcification become stress points that can lead to cusp tears. Extensive research over the past 3 decades has led to improved techniques of tissue preservation. Low- or zero-pressure fixation techniques combined with anti-mineralization treatment have led to significant gains in bioprosthesis durability. This has resulted in a dramatic shift over the past decade away from mechanical prostheses and lowering of the age threshold for bioprostheses.

The most commonly used stented xenograft in the United States is the Carpentier-Edwards PERIMOUNT Pericardial Valve (Edwards Lifesciences). The most recent design iteration of this valve, the Magna valve, purports to maximize hemodynamics

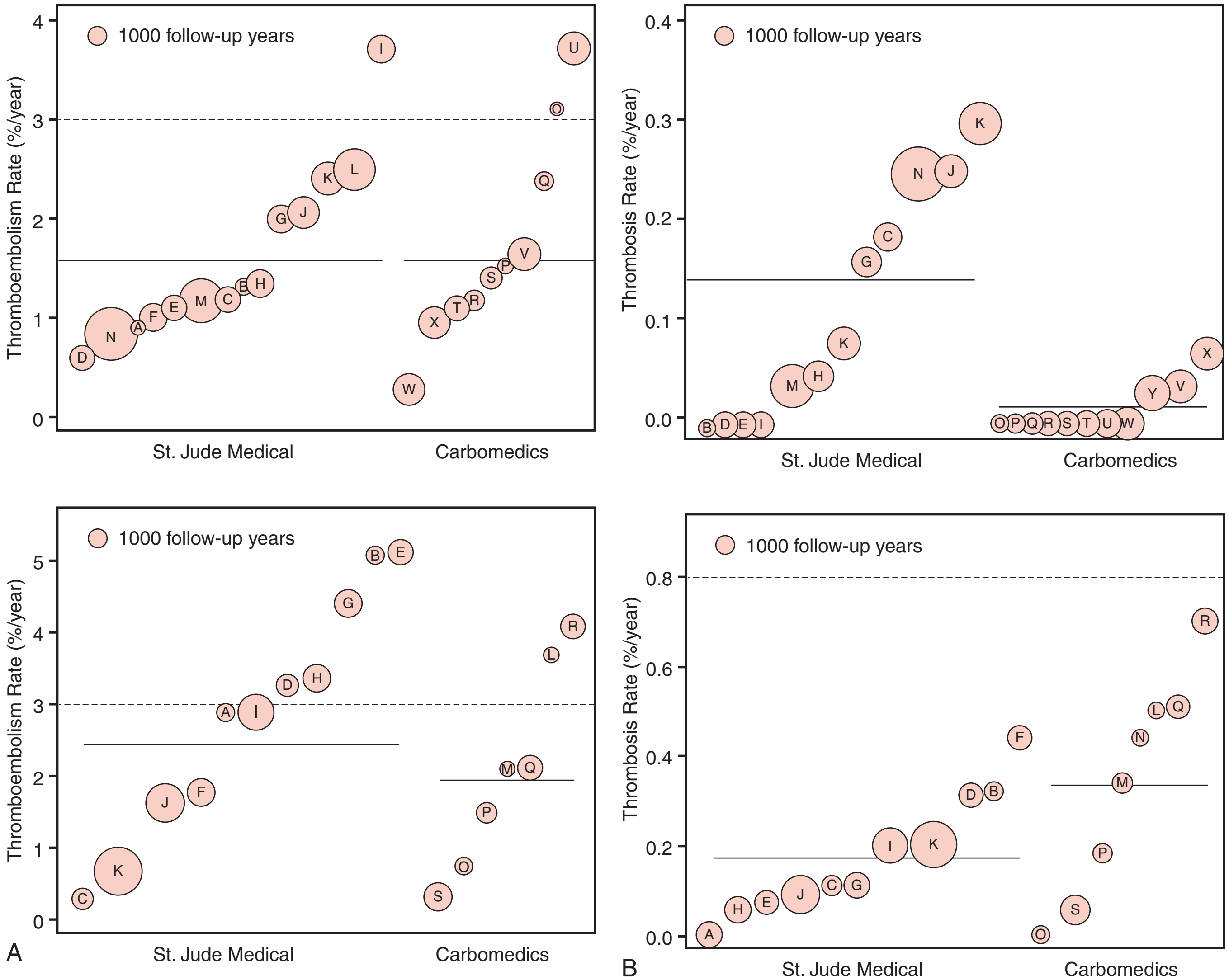


Figure 47–4 Valve-related complication rates of two types of mechanical valves—St. Jude Medical versus Carbomedics. Each circle represents a different study. **A,** Aortic. **B,** Mitral. (From Grunkemeier GL, Wu Y: "Our complication rates are lower than theirs": Statistical critique of heart valve comparisons. J Thorac Cardiovasc Surg 2003;125:290-300.)

through a true supra-annular design. Stented porcine valves currently marketed in the United States include versions of the Carpentier-Edwards Porcine valve (Edwards Lifesciences); the Hancock (I, II, and MO) and Mosaic valves (Medtronic); and the recently approved Biocor valve (St. Jude Medical). Durability data are discussed separately for aortic and mitral valve prostheses.

Stentless Xenografts

Stentless xenograft bioprostheses were developed to mimic the near-native hemodynamics of homografts and autografts while maintaining the ease of use and off-the-shelf convenience of stented bioprostheses. Eliminating the stent permits a larger valve to be inserted but increases the surgical complexity to some degree. Stentless valves can be inserted by one of several techniques. In a *subcoronary* implantation the valve is seated within the native aortic root. This typically requires two suture lines—a proximal suture line at the annulus and a distal one to secure the valve and commissures to the sinuses of Valsalva. The *hemi-root* or *full-root* techniques involve replacing part of the patient's aortic root with the bioprosthesis. The full root technique usually requires coronary reimplantation. Whichever technique is used, the implantation of a stentless valve is technically more challenging than that of a stented valve. Once implanted, stentless valves have an excellent hemodynamic profile and there is some evidence that they promote greater regression of LV hypertrophy.[21,22] The technical challenge and the lack of data showing an advantage with regard to hard endpoints have limited the adoption of stentless valves since their introduction in the early 1990s. Although some centers have adopted stentless valves as their valve of choice in the aortic position, most limit their use to specific indications, such as a small aortic annulus or diseased root.

Three stentless aortic valves are currently marketed in the United States. The Medtronic Freestyle and the Edwards Prima Plus are both delivered as full porcine aortic roots with the coronaries ligated and a cloth covering of the annulus. They can be used for a full root replacement or can be

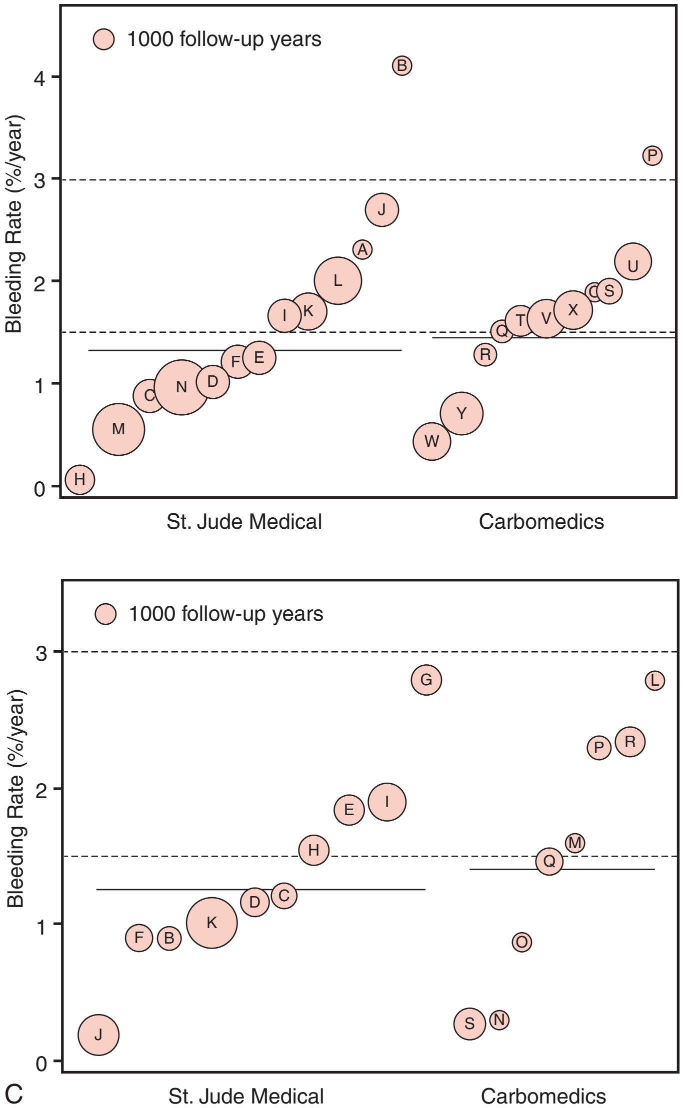


Figure 47–4, cont'd

trimmed for subcoronary implantation. The Toronto Stentless SPV valve (St. Jude Medical) is designed only for subcoronary implantation.

Homografts

Homograft valves have been used in the aortic position since the early 1960s following pioneering work by Ross and Barrett-Boyes. A variety of earlier preservation techniques have been replaced by cryopreservation. Homografts share many of the advantages of stentless valves including excellent hemodynamics and can also be used as full root or subcoronary implants. They appear to have a greater resistance to infection and are therefore commonly used in the setting of endocarditis. The primary limitation of homografts has been availability and storage requirements. Utilization of homografts appears to be declining; the most recent data indicate that their durability is not significantly better than modern-day bioprostheses.[23] Homografts tend to calcify as they fail, making reoperation in patients who have received full root replacements difficult.

Efforts to use mitral valve homografts have not been successful.[24] These efforts have been limited by the complex geometry of the mitral valve and accelerated degeneration. The increased utilization of valve repair and improvement in bioprostheses have also led to a decline in interest in this approach.

Postoperative Care

The postoperative care of patients undergoing valvular surgery must be tailored to the individual patient's specific condition. The immediate postoperative period is focused on maintaining an adequate cardiac output and monitoring for bleeding. Many, if not most, valve patients are candidates for a so-called "fast-track" protocol in which the anesthetic management is designed to permit extubation within 1 to 6 hours of arrival in the ICU, once hemodynamic stability and hemostasis have been achieved.

An increasing proportion of patients have decreased ventricular function, so it is not uncommon that patients will arrive in the ICU on inotropic support. In most patients the support can be weaned over the first 24 hours or so, but occasionally, in those with poor function, this process can take longer.

Pulmonary hypertension, if present, must be addressed carefully to protect the right ventricle, which is more difficult to protect and is therefore particularly vulnerable to myocardial stunning. Maneuvers may include avoiding hypoxia or hypercarbia; avoiding α-agonists; and use of pulmonary vasodilators, such as milrinone or, in severe cases, inhaled nitric oxide.

Patients with severe LV hypertrophy and diastolic dysfunction warrant careful postoperative hemodynamic management. These patients will often need aggressive volume resuscitation and require higher than expected intracardiac filling pressures to maintain an adequate stroke volume. An occasional patient with severe hypertrophy may develop dynamic outflow tract obstruction ("suicide ventricle"). In addition to maintaining adequate preload, inotropic agents should be avoided and peripheral vasoconstrictors should be used if necessary to maintain systemic blood pressure. If pacing is necessary, atrioventricular pacing is preferred because the hypertrophied ventricle will usually benefit from atrial contraction.

The next few days in the hospital course are typically focused on diuresis, rhythm management, reinstitution of cardiac and noncardiac medications, pulmonary toilet, mobilization, and anticoagulation. The incidence of postoperative atrial fibrillation is higher in valve patients than in coronary patients.[25,26] Preoperative prophylactic regimens have been proposed but are not widely used. Postoperative AF protocols vary from one institution to another but include β-blockers; amiodarone; calcium channel blockers; and, less commonly, digoxin.[27,28] Transient heart block is not uncommon, so most surgeons will place temporary pacing wires at the time of surgery. Most of the time this will resolve as edema subsides and electrolyte imbalances are corrected. Occasionally, however, a permanent pacemaker is required before discharge. It can be difficult to determine when to proceed with pacemaker implantation, but it is reasonable to wait 5 to 7 days for signs of recovery of the rhythm.

All patients with mechanical valves, most mitral valve patients, and those in atrial fibrillation will be anticoagulated

in the immediate postoperative period. Warfarin is usually initiated soon after surgery. Some surgeons are reluctant to bridge with IV heparin for fear of bleeding and tamponade. At a minimum, patients with mechanical mitral valves should be considered at high risk for early thromboembolism and should receive IV heparin if they are not therapeutic within a few days of surgery. Most centers still anticoagulate patients undergoing mitral valve repair, although some high-volume centers have chosen to be selective, using aspirin alone in younger, healthier patients with normal sinus rhythm and good ventricular function. Another area of controversy is whether to anticoagulate patients with aortic bioprostheses.[29-32] A survey indicated that most patients are not being anticoagulated in the absence of other indications.[33]

A baseline postoperative echocardiogram is usually performed before discharge in patients undergoing valve repair or stentless valve replacement. Predischarge education regarding antibiotic prophylaxis and anticoagulant therapy is important.

AORTIC VALVE SURGERY

Overview

Aortic valve replacement is the most commonly performed valve operation. It has been shown to be an effective therapy in all age groups including the very elderly (older than 90 years).[34] The most common etiologies for AS are calcific degeneration, rheumatic disease, and congenital bicuspid valves. The most common causes of pure aortic regurgitation (AR) include annulo-aortic ectasia and associated dilatation of the aortic root, endocarditis, aortic dissection, and rheumatic disease. The indications for surgery depend on the pathophysiology and symptoms. The choice of prosthesis can be difficult and depends on multiple clinical and lifestyle considerations. Early and late outcomes are generally quite good, even in high-risk patients.

Indications

Aortic Stenosis/Mixed Aortic Valve Disease

The indications for aortic valve surgery in pure AS and mixed disease are fairly well established[7] and are described in greater detail elsewhere. Current class I indications include severe AS with symptoms or signs of LV dysfunction, as well as other concomitant cardiac surgery. AVR is also recommended (class IIa) in patients with moderate AS undergoing CABG or other valve surgery to decrease the risk of early reoperation for progression of the AS. Intervening in mild AS at the time of CABG is more controversial but has been suggested, especially in patients who appear to be at high risk for progression, such as those with significant calcification.[35-39] Other possible but controversial indications for AVR include asymptomatic patients with normal ventricular function and severe AS (valve area < 0.6 cm^2), those with severe AS but abnormal response to stress testing (e.g., hypotension), and those with risk factors for more rapid progression.

Patients with poor LV function (ejection fraction < 30%) with AS will often present with relatively low gradients. Recent data suggests that carefully selected patients in this subgroup will benefit from surgery.

Aortic Regurgitation

The natural history of AR makes the timing of aortic valve surgery more difficult. Patients can remain relatively asymptomatic until significant ventricular damage has occurred. Class I indications include symptomatic severe AR and asymptomatic severe AR with LV dysfunction. Surgery is also recommended (class IIa) in asymptomatic patients with normal LV function but severe dilatation (end-diastolic or systolic dimensions of > 75 mm or > 55 mm, respectively). Severe, and probably moderate, AR should be corrected at the time of CABG or other valve surgery.

Aortic Valve Replacement

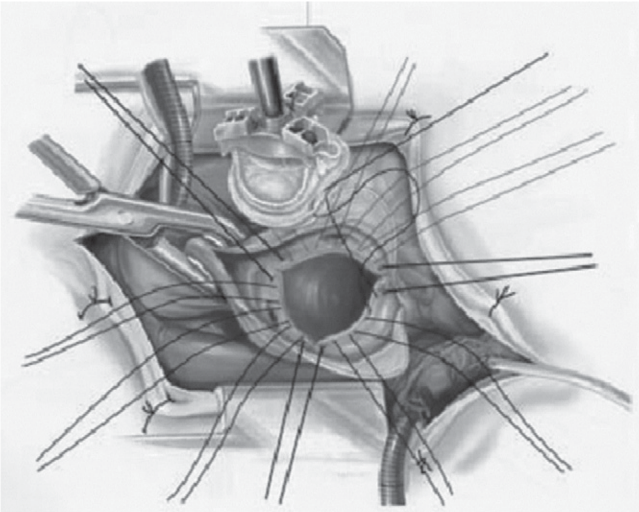
Surgical Technique

The steps involved in replacing the aortic valve are fairly well established (Fig. 47–5A). Routine scanning of the aorta is increasingly used before cannulation for cardiopulmonary bypass, usually via the distal aorta and right atrium. The aorta is clamped, and the heart is protected with hyperkalemic cardioplegia solution delivered anterograde in the aortic root or coronary ostia or retrograde via the coronary sinus, or both. This is usually supplemented with mild systemic or topical hypothermia, or both. An incision is made in the proximal aorta, and the valve is inspected. Débriding a highly calcified valve and annulus can be a significant challenge, and careful attention must be paid to removing all the calcium while maintaining adequate annular tissue and removing all loose debris that can later embolize. The calcium will sometimes continue up the aortic wall, and localized endarterectomies may be required.

Once the annulus is fully débrided, the valve is secured with sutures. The specific suture technique (pledgets versus no pledgets, interrupted versus running, everting versus noneverting, supra-annular versus intra-annular) can vary from surgeon to surgeon. The suturing technique does not vary significantly between stented xenografts and mechanical valves. Subcoronary implantation of stentless valves, homografts, or even autografts require a second outflow suture line to secure the valve to the aortic wall. The largest-size valve that can be comfortably implanted is usually selected. If the annulus is small, the surgeon can enlarge it using a patch to permit a larger prosthesis to be implanted or use a stentless valve.

The aortotomy is sutured closed, air is evacuated from the heart, and the cross-clamp is removed. The patient is weaned off of cardiopulmonary bypass, heparin is reversed with protamine, and the cannulae are removed. Temporary epicardial pacing wires and chest drains are placed before sternal closure.

An aortic root replacement with coronary reimplantation (Bentall procedure) may be performed if there is concomitant aortic root disease (dilatation, calcification) or if the surgeon chooses to implant a stentless prosthesis or homograft as a full root. The aorta is resected from the annulus to ascending aorta (or further distally if indicated). The coronary ostia are preserved as buttons. A valved conduit (mechanical or stented valve attached to a Dacron tube graft), stentless valve (porcine root), or homograft is selected and secured proximally and distally to the annulus and aorta, respectively. The coronary buttons are sutured to holes created in the conduit.



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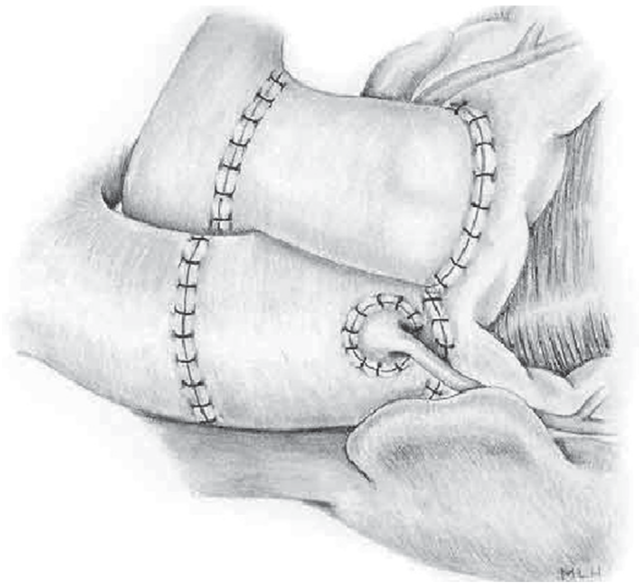


B

Figure 47–5 (*See also Color Plate 47–5*.) Surgical technique of aortic valve replacement. **A,** Stented xenograft. **B,** The Ross ("Pulmonary Autograft AVR") Procedure – The patient's pulmonary valve and root are translocated into the aortic position and replaced with a homograft. The figure shows a completed procedure as seen by the surgeon standing to the patient's right. The patient's head is to the left and feet are to the right. The confluence of the superior vena cava and right atrial appendage is at the bottom of the figure. Moving up (from the patient's right to left) are (1) the pulmonary autograft with its distal suture line to the ascending aorta and proximal suture line to the aortic annulus; the right coronary artery has been reimplanted as a button, the left coronary button is posterior and not visualized; (2) the pulmonary homograft with its distal suture line to the confluence of the pulmonary arteries and the proximal arteries and the proximal suture line to the right ventricular outflow tract.

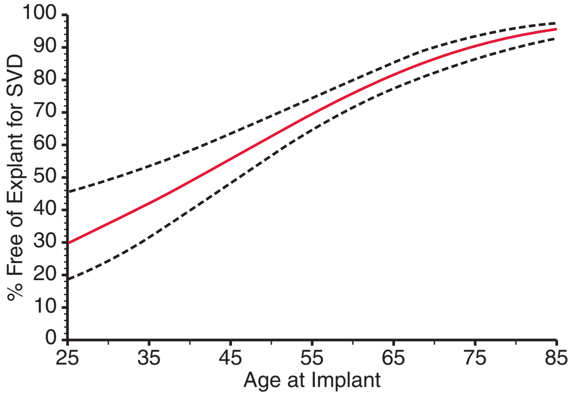


Figure 47–6 Age dependence of structural valve degeneration of Carpentier-Edwards pericardial valve in the aortic position.[70]

The pulmonary autograft or Ross procedure is usually performed as an aortic root replacement using the patient's own pulmonary valve/artery as the prosthesis (see Fig. 47–5B). The implant is similar to other root replacements except that the annulus and sinotubular junction are often reinforced with prosthetic material to prevent late dilatation. A pulmonary homograft is usually used to reconstruct the right ventricular outflow tract.

Choice of Prosthesis

Selecting the most appropriate prosthesis in a patient undergoing AVR is a complex decision with significant long-term consequences for the patient. As noted in Table 47–3, the available prostheses differ significantly with regard to key parameters, such as the need for anticoagulation, freedom from thromboembolism, durability, ease of operation, hemodynamic performance, and resistance to infection. Although broad, age-based guidelines do exist, the final choice should be tailored to the individual patient and should take into consideration multiple factors in addition to age, such as concomitant diseases (especially those affecting life expectancy), general lifestyle, physical activity, surgeon expertise, and ultimately overall patient preference.

The primary factor in prosthesis selection does, however, remain patient age. Elderly patients have lower life expectancies and tend to be less physically active. Younger patients, on the other hand, place a greater demand on the prosthesis with regard to durability and hemodynamic performance. Age has long been recognized as the primary determinant of bioprosthesis calcification and thus durability. Long-term follow-up of the Carpentier-Edwards pericardial valve confirms a strong correlation between age at implant and the likelihood of explant at 15 years (Fig. 47–6). The traditional age threshold for a bioprosthesis has been between 65 and 70 years. The actual lifetime likelihood of reoperation for structural valve dysfunction in a 65-year-old is less than 10%. Given the excellent durability of modern bioprostheses, it is difficult to justify implantation of a mechanical valve in any elderly patient. The fact that the patient is already on warfarin for another indication, such as atrial fibrillation, does not justify the use of a mechanical valve because it converts a relative indication for low-level anticoagulation to an absolute indication for higher levels of anticoagulation. It also eliminates

the option of discontinuing anticoagulation in the event of a major bleeding episode. Even the presence of another mechanical valve does not mandate a second mechanical valve because risk of thromboembolic and bleeding complications is higher with two mechanical valves than one.

The choice of prosthesis in patients younger than 65 is more complex and controversial. Traditionally these patients would receive a mechanical valve. The improvement in bioprosthesis durability and the decrease in the operative risk of replacing a failed prosthesis have led to an increase in the number of patients younger than 65 receiving bioprostheses including many patients in their 50s and some even younger. Women of child-bearing age pose a particular dilemma and often choose a bioprosthesis to avoid warfarin with the understanding that they will face at least one reoperation in their lifetime.

By eliminating the stent and most of the prosthetic material, stentless valves such as the Toronto SPV, Freestyle, and Prima Plus valves allow implantation of a larger valve than would be possible with a stented xenograft. The most commonly implanted stentless valve sizes are 25 to 29 mm, while most stented valve patients receive a 21- to 25-mm valve. In addition, when matched for size, the hemodynamic profiles of stentless valves are superior to stented valves, especially at the smaller sizes.[40] These differences are even greater when measured during exercise or pharmacologic stress.[41] These hemodynamic benefits may justify the use of stentless valves in younger, more active patients in whom a bioprosthesis is being considered. Whether this hemodynamic benefit translates into real clinical benefit remains controversial. Although the 10-year follow-up with the Freestyle is excellent,[42] duration of follow-up is not adequate to show improved durability. Some data suggest improved LV mass regression,[43,44] but only limited data suggest that this translates into greater survival.[45] Some data suggest fewer thromboembolic complications.[46] Despite these data, the specific indications for the use of a stentless valve are not well defined. At this point their use is primarily driven by surgeon preference.

The use of homografts as a primary aortic valve substitute has declined in recent years. Like stentless valves, homografts have excellent hemodynamics and are resistant to thromboembolism and infection. Recent data, however, suggest that their durability is not significantly better than stented xenografts. Without a durability advantage, it is difficult to justify their routine use given their limited availability and the cumbersome storage requirements. Their resistance to infection, however, makes them an excellent choice for patients with endocarditis.

The pulmonary autograft or Ross procedure involves replacing the aortic valve with the patient's own pulmonic valve, which in turn is replaced with a homograft or a stentless xenograft. The advantages are near-native hemodynamics and excellent autograft durability. The disadvantages are the high degree of technical complexity and need for reoperation for the homograft. On the basis of the data from the Ross Procedure International Registry, the Ross procedure peaked in popularity in the mid to late 1990s and procedure volume has declined since then. Several centers continue to report excellent results,[47,48] but it is now primarily a procedure for pediatric patients (where the potential for growth is important) and young adults in their 20s and 30s when no other good alternatives exist.

Patient-Prosthesis Mismatch

The concept of patient-prosthesis mismatch (PPM) remains hotly debated. Strictly speaking, it is defined as a prosthesis that is too small relative to the patient's size and provides residual obstruction to flow despite normal prosthesis function. The most common measure is the indexed effective orifice area (EOAI = EOA/BSA). The incidence of PPM depends on the cut-off used. Severe PPM defined as an EOAI < 0.65 cm^2/m^2 occurs in up to 10% of patients and moderate PPM in up to 70%.[49] Some authors argue that PPM is not clinically relevant—that LV ventricular mass regression and early and late cardiac events are not affected.[50-52] Others, led by Pibarot and colleagues, argue vigorously that PPM dramatically affects LV mass regression, operative mortality, late functional status, heart failure, and mortality.[49,53] Because surgeons will routinely attempt to implant the largest possible prosthesis, the debate can ultimately be distilled down to the question of whether the surgical technique should be modified to avoid PPM. Specific maneuvers include aortic annular enlargement and use of a stentless prosthesis. Opponents argue that these maneuvers carry additional operative complexity and risk and are therefore not justified.

Aortic Valve Repair

Selected patients with aortic insufficiency may be candidates for aortic valve repair, although they are rarely performed. Patients will occasionally present with isolated cusp perforation (iatrogenic, healed endocarditis) or cusp prolapse. These valves can be repaired using a pericardial patch over the perforation or plicating the prolapsing segment. Patients with retracted but mobile and noncalcified cusps from rheumatic disease can undergo leaflet extension with pieces of pericardium. Patients with noncalcified congenital bicuspid valve disease and AR are offered repair at some centers.[54-56] This typically involves resection of the redundant cusp and commissural plication.

Patients with normal cusps and aortic insufficiency secondary to concomitant aortic root dilatation can avoid valve replacement by undergoing one of several "valve-sparing" aortic root operations. These operations, pioneered by Yacoub[57,58] and David,[59,60] seek to reestablish the 3-D support of the native valve to permit adequate coaptation. Although technically difficult, these operations have good results in selected patients when performed at experienced centers.

Results

Early

The operative mortality for patients undergoing aortic valve replacement has declined steadily and is now 3.3% for isolated AVR and 5.5% for AVR CABG (STS 2005). A young, otherwise healthy patient with good ventricular function can be offered the procedure with a predicted operative mortality of 1% (STS Risk Calculator). Elderly patients[29,34,61,62] and those with decreased ventricular function[63-65] do surprising well following AVR for AS, presumably because of the immediate benefits of unloading the left ventricle. The operative risk does, however, increase in the presence of multiple-risk factors including age,

female gender, poor LV function, class IV heart failure, coronary artery disease, renal failure, endocarditis, urgent/emergent surgery, and reoperation. The most common causes of operative mortality are myocardial failure and stroke.

The most common complications following aortic valve surgery are similar to those of other cardiac surgery and include stroke (2% to 4%), deep sternal wound infection (1% to 2%), reoperation for bleeding (1% to 3%), and myocardial infarction (1% to 5%). Transient heart block, presumably as a result of traction or edema of the bundle of His in the vicinity of the right-noncoronary commissure, is not uncommon. It usually resolves within 5 to 6 days of surgery. The risk of complete heart block requiring pacemaker insertion is 3% to 5%.[66,67]

Late

Long-term survival following AVR depends on the patient's characteristics and comorbidity. Estimated 10-year survival can range from 85% in younger, healthier patients to 40% in elderly patients with CAD, class IV CHF, and decreased LV function.[68] Very elderly patients undergoing AVR have survival rates similar to their peers without aortic valve disease.[69] Approximately 40% of deaths following AVR are valve related, and another 20% are related to nonvalvular cardiac causes. There does not appear to be a clinically significant difference in survival between mechanical and biologic valves when age and other risk factors are controlled.

Freedom from reoperation depends on the prosthesis and age. Although they do not degenerate, modern mechanical valves do have a finite reoperation rate of 0.5% to 1% per year from endocarditis, pannus overgrowth, and thrombosis. Actual freedom from reoperation of modern bioprostheses at 15 years approaches 100% in elderly patients older than 70 years. It can be as low as 50% in patients younger than 50 years.[70,71]

MITRAL VALVE SURGERY

Overview

Although aortic valve surgery remains the most common valve operation (see Fig. 47–1C), the field of mitral valve surgery has been very dynamic with several important trends and advances in the past decade.[72] The incidence of rheumatic heart disease has declined, and techniques of percutaneous balloon mitral valvuloplasty have improved. These have led to a decline in the number of patients undergoing surgery for mitral stenosis. In contrast, the number of patients undergoing mitral valve repair, nearly all for mitral regurgitation, has doubled in the past decade (see Fig. 47–1C). A greater understanding of the benefits and techniques of mitral valve repair for degenerative disease has contributed to this trend, although mitral valve repair remains underused.[6] Other contributing factors include (1) broadening indications for surgical intervention including asymptomatic patients with normal ventricles; (2) a greater understanding of the pathophysiology, clinical course, and role of mitral valve surgery in ischemic MR; and (3) a greater acceptance of isolated or concomitant mitral valve repair in patients with poor ventricular function.

Anatomy

The surgical anatomy of the mitral valve is shown in Figure 47–7. The leaflets are divided into eight segments. The posterior leaflet is divided into three segments (P1, P2, P3) on the basis of anatomically distinct scallops. Each anterior leaflet segment (A1, A2, and A3) is defined by its corresponding posterior segment. The anterolateral commissure (Ac) and posteromedial commissure (Pc) have small but distinct leaflet scallops. The subvalvular apparatus consists of the papillary muscles and chordae tendinea, which are further subdivided into primary/marginal (attached to free margin), secondary (attached to underbelly of leaflet), and tertiary/basal (attached to annulus).

Carpentier's Functional Classification

Although several systems for classifying mitral valve dysfunction have been proposed, Carpentier's functional classification of mitral regurgitation based on the "pathophysiologic triad" (etiology → lesions → dysfunction) is the most robust (Table 47–6). Each etiology (degenerative, rheumatic, ischemic, dilated cardiomyopathy, endocarditis, etc.) results in one or more lesions of the annulus, leaflets, or subvalvular apparatus. These lesions result in a specific type of dysfunction on the basis of leaflet motion (see Fig. 47–7A). In a normally functioning mitral valve, the leaflets come together within the valve orifice, resulting in a surface of coaptation. The free margins of the leaflets remain below the plane of the annulus.

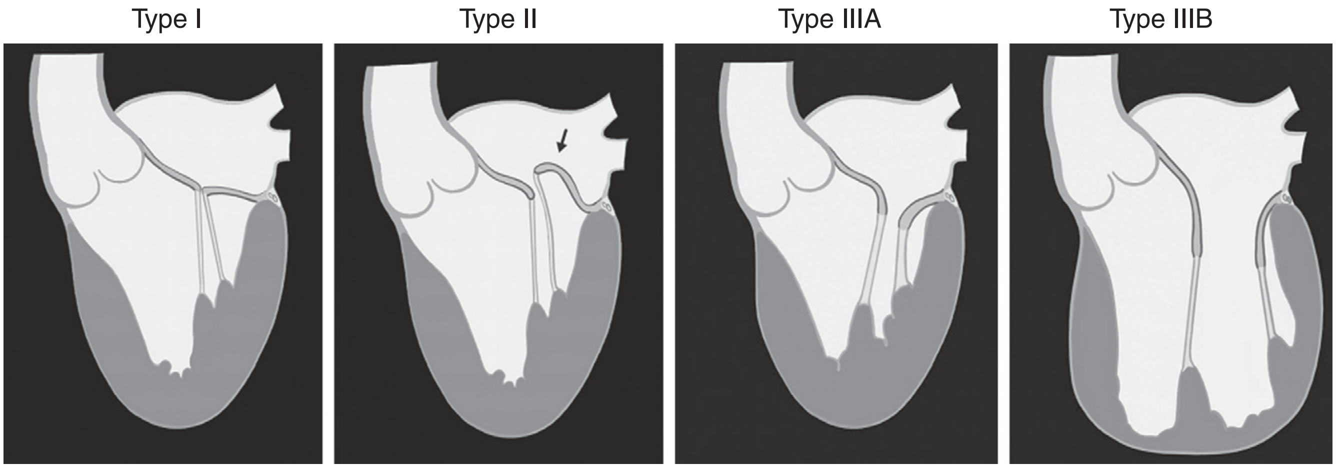
In *type I* dysfunction, the leaflets exhibit normal motion. The regurgitation results in annular dilatation, which prevents coaptation, or from leaflet perforation.

Type II dysfunction results from *leaflet prolapse,* in which the free margins of the involved portions of the leaflets rise above the plane of the annulus into the left atrium, preventing leaflet coaptation. The most common lesions resulting in leaflet prolapse and type II dysfunction include chordal elongation or rupture due to degenerative changes.

Finally, *type III* dysfunction results from *restricted leaflet motion*. Here, the free margins of portions of one or both leaflets are pulled below the plane of the annulus into the left ventricle, preventing them from rising up to the plane of the annulus and coapting during systole. The restricted leaflet motion can occur during both systole and diastole, related to valvular or subvalvular pathology (rheumatic fibrosis)—referred to as type IIIA dysfunction. Type III dysfunction more commonly occurs when abnormal ventricular geometry or function leads to papillary muscle displacement, which pulls the otherwise normal leaflets into the ventricle. This is known as type IIIB dysfunction and usually results from prior myocardial infarction (ischemic) or severe ventricular dilatation and dysfunction. Frequently, types I and IIIB dysfunction (except leaflet perforation) are referred to as "functional" MR because they occur in the absence of structural abnormalities of the valve.

Preoperative Evaluation

A high-quality echocardiogram is particularly important in the preoperative evaluation of patients with mitral valve disease. Transesophageal echocardiography may be necessary to obtain all of the important anatomic and physiologic data.



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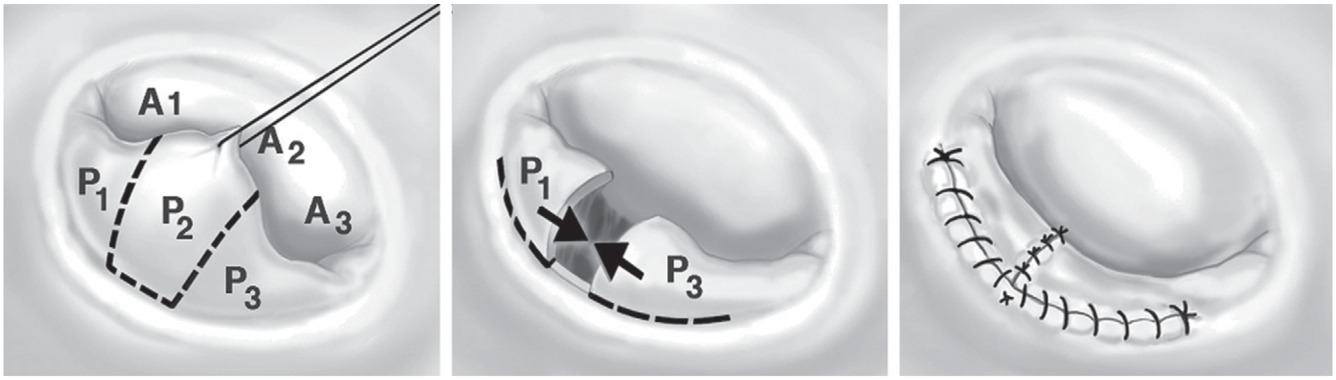


B

Figure 47–7 (*See also Color Plate 47–7.*) Principles of mitral valve repair. **A,** Carpentier's functional classification of mitral regurgitation. **B,** Quadrangular resection of the posterior leaflet with sliding valvuloplasty for P2 prolapse.

The severity of MS or MR may have already been established, but more quantitative assessment of MR (PISA, ERO, RV) may be particularly useful in patients with functional MR (type I, IIIB). The specific type of dysfunction (Type I, II, IIIA, or IIIB) should be determined preoperatively by carefully assessing the motion of each segment of each leaflet. The etiology can usually be determined with a combination of history, physical examination, and echocardiography. Distinguishing between specific lesions (e.g., ruptured versus elongated chord) is less important because the likelihood of repair and surgical techniques is determined by the etiology and type of dysfunction. Extensive mitral annular calcification is an important finding because it can significantly increase the complexity of the surgical procedure. Other echocardio-

Table 47–6 Carpentier's Functional Classification of Mitral Regurgitation

Dysfunction	Leaflet Motion	Lesions	Common Etiologies
Type I	Normal	Annular dilatation Leaflet perforation	Dilated cardiomyopathy Ischemic (basal infarction) Endocarditis
Type II	Increased (prolapse)	Chordal elongation Chordal rupture Papillary muscle Elongation Papillary muscle rupture	Degenerative Endocarditis Ischemic (PM infarction)
Type III	Restricted		
A	Systole and diastole	Leaflet thickening and retraction Subvalvular thickening and shortening	Rheumatic
B	Systole	Papillary muscle displacement Annular calcification	Dilated cardiomyopathy Ischemic

graphic characteristics, such as atrial and ventricular dimensions, ventricular function, estimated pulmonary artery pressures, and the status of the other valves remain critical.

Indications

Mitral Regurgitation

The indications for surgical intervention in mitral regurgitation have steadily expanded as the results of mitral valve repair have improved. Class I indications include severe MR in the presence of symptoms or LV dysfunction. On the basis of recent natural history data,[73] surgery is also recommended (class IIA) for asymptomatic patients with severe MR and normal LV function as long as valve repair is deemed likely with a reasonable operative risk. Because the likelihood of repair is lower, surgery is usually deferred in patients with rheumatic disease until the onset of symptoms or LV dysfunction.

Poor LV function and class III-IV heart failure were once considered an absolute contraindication to mitral valve surgery. This was based on data showing poorer early and late outcomes in these patients, especially when they undergo non–chordal-sparing valve replacement. It was theorized that the mitral regurgitation served as a "pop-off" valve, providing a low-afterload circuit (the left atrium) for the failing ventricle. This concept is now known to be false; it is clear that MR causes volume overload and *increases* wall stress on the ventricle. Severe ventricular function is no longer an absolute contraindication to mitral valve surgery. Recent data from Bolling[74] and others, however, have demonstrated that patients with severe LV function can undergo valve repair with a downsized annuloplasty with reasonable early outcomes. Whether valve repair in this setting improves long-term outcomes is unknown, so this remains a class IIB indication.[75]

Mitral Stenosis

The indications for surgery are more conservative than for mitral regurgitation for several reasons. First, the etiology is usually rheumatic heart disease which has a slower, more predictable natural history. A smaller proportion of patients are candidates for mitral valve repair so the additional risks associated with a mitral valve prosthesis must be taken into consideration in the remaining patients. Finally, patients who are good candidates for percutaneous balloon mitral valvuloplasty (PBMV) can avoid surgery, at least for the medium term. Currently accepted indications for surgery include symptomatic moderate-to-severe MS when PBMV is either unavailable or contraindicated (thrombus, significant MR, unfavorable morphology). Mildly symptomatic patients with severe pulmonary hypertension should also be considered for surgery before the onset of right heart failure.

Mitral Valve Repair

Principles

The techniques of mitral valve repair are based on certain fundamental principles developed by Carpentier and others over the past 35 years. They start with the notion that, in theory, any regurgitant valve with adequate, pliable, noncalcified leaflet tissue can be repaired as long as a systematic approach, based on pathophysiologic principles described earlier, is applied. The likelihood of a successful repair depends on surgeon experience and the complexity of the repair, which in turn depends on the etiology, type of dysfunction, and the distribution of lesions among the various anatomic components of the valve (leaflets, annulus and subvalvular apparatus). The complexity can range from a simple annuloplasty to a complicated Barlow's valve repair involving interventions to multiple leaflet segments. Although it can vary from patient to patient, generally anterior leaflet pathology is more difficult to repair than posterior leaflet pathology and rheumatic valves are more challenging than degenerative valves.

The first step in any repair is precise, systematic *valve analysis*, initially by TEE and then by direct assessment (see Fig. 47–7B). The central goal is to determine the type of dysfunction of each of the eight leaflet segments (A1-A3, P1-P3, Ac, and Pc). This is done by pulling the free margins of the leaflet segment up using a hook and determining whether the leaflet motion is normal (type I), excessive (type II), or restricted (type III). The annulus is assessed separately, noting it size and symmetry, as well as any calcification. Once the valve analysis is complete, the operative plan is established. The specific techniques used depend on the type of dysfunction and are described as follows.

Annuloplasty

Implantation of a prosthetic annuloplasty ring is an essential part of nearly all mitral valve repairs. The exceptions include the occasional patient with endocarditis involving only the body of a leaflet. Nonprosthetic annuloplasty techniques using suture or pericardium do not have a role in modern mitral valve repair because the results with these techniques are well below those of prosthetic rings.

The primary purpose of the annuloplasty is to restore the annular dimensions, bringing the leaflets together and permitting a broad surface of coaptation—a critical element to a durable repair. It also stabilizes the annulus, taking stress off of sutures lines. An annuloplasty ring typically is constructed from a core material (silicone, metal) that determines its rigidity (flexible, semirigid, rigid) sheathed in a cloth material (Dacron, polyester) through which the sutures are placed. Annuloplasty rings come in numerous sizes, shapes (partial band, complete ring), and rigidity but can be broadly categorized as *remodeling* or *nonremodeling*.

A remodeling annuloplasty seeks to restore the size *and* physiologic ("D," "kidney") shape of the annulus in contrast to a restrictive, nonremodeling annuloplasty, which merely decreases the overall circumference of the annulus. Many surgeons, especially those who subscribe to the Carpentierian principles of valve repair, feel that a complete remodeling annuloplasty (e.g., Carpentier-Edwards Physio) should be performed in all repairs to assure a long-term durable result. Others favor partial or complete flexible rings (e.g., Cosgrove-Edwards Band). Most surgeons, however, now acknowledge that a remodeling annuloplasty is superior in patients with type IIIB MR secondary to ischemic disease or dilated cardiomyopathy. The size of the annuloplasty ring is determined by the height of the anterior leaflet and the intercommissural (or intertrigonal) distance. Patients with degenerative disease and type II dysfunction will typically receive a ring in the 32- to 40-mm range, while those with type IIIB dysfunction

from ischemic disease or cardiomyopathy will receive much smaller rings, in the 24- to 30-mm range.

Mitral annular calcification (MAC) is not an infrequent finding in patients undergoing mitral valve surgery, especially elderly patients and those with coronary artery disease. MAC poses serious challenges to the surgeon in both mitral valve repair and replacement. It can interfere with seating of the annuloplasty ring, restrict and distort leaflet tissue, and in severe cases extend deep into the subannular ventricular muscle. Ideally, all annular calcification is removed, en bloc prior to reconstruction and ring implantation. This is usually straightforward for discrete superficial nodules in the posterior annulus but becomes progressively more challenging if it involves the commissures and is more diffuse and deep. Carpentier has shown that complete en bloc excision of even massive MAC, with subsequent reconstruction of the atrioventricular junction, can be performed safely. Many surgeons, however, remain wary of this approach for fear it will lead to atrioventricular rupture, a dreaded complication that is usually fatal.

Leaflet Prolapse Repair Techniques (Type II)

Leaflet prolapse can be corrected through one of several approaches involving the leaflets and subvalvular apparatus. The specific technique depends on the specific prolapsing segment more than the actual lesion (chordal rupture, or chordal elongation). The ultimate goal is to leave an adequate amount of mobile, well-supported leaflet to participate in coaptation.

Posterior leaflet prolapse is usually treated by resecting the prolapsing segment and reapproximating the nonprolapsing segments (see Fig. 47–7B). This most commonly involves a *quadrangular resection* of a prolapsed P2 segment. If the resection is relatively small, the annular gap can simply be plicated and the cut edges reapproximated. Usually, however, a *sliding valvuloplasty* is recommended. Here, the remaining P1 and P3 segments are partially detached from the annulus and then reattached, stretching them across the annular gap, which can be decreased with so-called compression sutures. The sliding valvuloplasty technique has two advantages. It avoids the need to plicate a large annular gap, which can lead to kinking of the circumflex artery. During the process of detaching and reattaching the remaining segments, the surgeon can decrease the height of the posterior leaflet. Left alone, the excessively tall posterior leaflets seen in Barlow's disease patients can lead to a systolic anterior motion (SAM) in which the anterior leaflet is pushed into the LV outflow tract, causing obstruction.

Anterior leaflet prolapse can be corrected by resecting the prolapsing segment or reestablishing its subvalvular support. *Triangular resections* with direct reapproximation of the cut edges can correct small areas of prolapse, especially when there is redundant tissue, such as in Barlow's disease. There is a limit to how much anterior leaflet tissue can be resected before the remaining tissue is inadequate for coaptation, however. If redundant tissue is not present or large areas of prolapse exist, subvalvular support to these areas must be reestablished. *Chordal transfer* involves detaching normal secondary chords attached to the body of the anterior leaflet and reattaching them to the margin of the prolapsing segments. With *chordal transposition* the chords are detached, along with some leaflet tissue, from a normal portion of the posterior leaflet, and then flipped anteriorly and reattached to the prolapsing segment, after which the gap in the posterior leaflet is closed primarily. Finally, if no good chords are available, an *artificial chordoplasty* can be performed. The new chords are creating using Gortex sutures secured to the papillary muscle and prolapsing leaflet segment. Chordal shortening techniques, in which the length of the elongated chord is decreased by burying the excess into the papillary muscle, were abandoned when retrospective studies showed that they were less durable.

Correcting *commissural prolapse* can be particularly technically challenging. Sliding valvuloplasty techniques similar to those used on the posterior leaflet can be applied, but care must be taken to avoid distortion of the valve. Chordal support to the prolapsing commissure can also be established using the same techniques as in the anterior leaflet.

Restricted Leaflets Techniques (Type III)

In patients with type IIIA dysfunction, usually from rheumatic disease, the restricted leaflet motion results when the fibrotic process leads to thickening and fusion of the subvalvular structures and thickening and retraction of the leaflets, particularly the posterior leaflets. As long as adequate, pliable leaflet tissue is available, valve repair can successfully be performed with good long-term results, but this type of repair is not widely practiced outside of major valve repair centers. *Leaflet mobilization* is accomplished by resection of secondary chordae and splitting or fenestrating fused marginal chordae. *Leaflet enlargement*, typically to the posterior leaflet, can be performed by detaching the leaflet annulus and suturing a patch of autologous glutaraldehyde-fixed pericardium. Patients with rheumatic MS, pure or in combination with MR, are treated with *open commissurotomy*. The fused commissures are split sharply within a few millimeters of the annulus, and the associated fused chords are split down the papillary muscles or fenestrated.

Patients with type IIIB dysfunction, resulting from ischemic heart disease or dilated cardiomyopathy, have structurally normal leaflets that are restricted as a result of papillary displacement from ventricular dilatation and regional wall motion abnormalities. In order to reestablish an adequate surface of coaptation, the restricted leaflets must be brought toward each other. The final anteroposterior dimension of valve must be less than its original dimension, in order to overcome the fact that the restricted leaflets cannot rise to their normal systolic position just below the plane of the annulus.

This can be accomplished with a *downsized remodeling annuloplasty* alone. The intercommissural or intertrigonal distance and the anterior leaflet height are measured, and a ring 2 to 4 mm smaller is selected to achieve proper downsizing. Recently introduced rings specifically designed for type IIIB dysfunction—the asymmetric Carpentier-McCarthy-Adams EtLogix ring for ischemic MR and the Geoform ring for cardiomyopathy (both Edwards Lifesciences)—are "predownsized." In other words, they are designed to be more squat with a significantly reduced anteroposterior dimension relative to the intercommissural dimension, allowing good leaflet coaptation while maximizing the overall orifice area.

Although insertion of an annuloplasty ring alone suffices in the vast majority of patients undergoing repair for type IIIB MR, occasionally adjunctive techniques may be useful.

Resection of secondary chordae, particularly to the anterior leaflet, can increase leaflet mobility and correct the "hockey-stick" deformity seen in patients with severe leaflet restriction. Occasionally, prominent clefts between the posterior leaflet scallops will be splayed out by the leaflet restriction and closing these clefts can prevent small areas of residual MR. Other techniques, such as papillary muscle relocation and patch extension of the posterior leaflet, have been reported but are not widely used in this condition.

Other Techniques

The *edge-to-edge* or *Alfieri* technique involves suturing the free edges of the anterior and posterior leaflets together (usually at A2-P2), creating a double orifice mitral valve. The percutaneous application of this technique is being explored. The technique can correct prolapse in one leaflet by using the other leaflet's chordae. In the process, however, it decreases the mitral valve orifice area. No long-term data are available on the durability of this type of repair.[76] Early data, however, clearly document poor outcomes in the absence of a concomitant annuloplasty[77] and in ischemic MR.[78]

Mitral Valve Replacement

Despite the broadening indications for mitral valve repair, the evidence base supporting valve repair when feasible, and the increased availability of surgeons proficient in these techniques, the majority of patients undergoing mitral valve surgery still undergo valve replacement. Some of these valve replacements are being performed in patients with valves that are not repairable, such as those with advanced rheumatic disease with calcification, endocarditis with extensive leaflet destruction, or ruptured papillary muscles following myocardial infarction. However, many of these replaced valves could have been repaired by experienced mitral valve repair surgeons. In particular, many surgeons are reasonably comfortable repairing valves with isolated posterior leaflet prolapse but proceed with valve replacement when they encounter prolapse of the anterior leaflet. Experienced surgeons, however, can repair > 90% of degenerative valves whether the anterior leaflet, posterior leaflet, or both are involved.

Chordal-Sparing Mitral Valve Replacement

In the early days of mitral valve replacement, the entire valve including leaflets and chordae were resected before implantation of the valve. In the late 1970s and 1980s, however, it became clear that the subvalvular apparatus was an integral component to global ventricular function and this practice frequently led to decreased LV function following valve replacement. *Chordal-sparing* techniques were developed and shown to be superior in terms of preservation of LV function, as well as early and late outcomes.

The posterior leaflet is now almost always left intact and plicated within the posterior suture line. The chordal apparatus to the anterior leaflet can also be preserved by resecting an elliptical portion of the body of the leaflet, splitting the remaining rim of leaflet with attached chordae in two and reattaching them to the anterior annulus. Occasionally, in patients with extensive rheumatic fibrosis, calcification, or endocarditic destruction, it may be impossible to preserve the chordal apparatus. In these cases artificial Gortex chords can be used to reestablish papillary muscle-annular continuity.

The actual implantation of the valve is similar to a prosthetic aortic valve replacement and can be performed using a variety of suturing techniques (interrupted versus running, pledgeted versus nonpledgeted, everting versus noninverting). As with aortic valve replacement, complete débridement of annular calcification is important to prevent perivalvular leaks, although this must be done with great care to avoid atrioventricular disruption, a highly fatal complication.

Choice of Prosthesis

The choice of valve prosthesis is somewhat less complicated in the mitral position than in the aortic posi-tion. For example, the options are limited to mechanical valves or stented xenografts (porcine or pericardial). In addition, although the durability of mitral bioprostheses has improved significantly, it is not yet good enough to justify routine use in middle-aged adults. Patients younger than 65 typically receive mechanical valves and those 65 and older receive biologic valves. The age threshold can certainly be lowered in selected situations. Patients with coronary artery disease, poor LV function, or comorbidities leading to decreased life expectancy may be candidates for biologic valves. Younger patients who cannot or choose not to take warfarin may also receive a biologic valve, but they need to understand that they almost certainly will face one, if not two, reoperations in their lifetime. Whenever possible, of course, a valve repair would be preferable in patients of all age groups.

Results

Early

The operative risk of mitral valve surgery varies significantly depending on the patient profile and operation. It can be as low as 1% for young, healthy patients undergoing elective mitral valve repair for degenerative disease or > 50% in an ill elderly patient undergoing emergent surgery for endocarditis. The overall operative mortality rates for isolated mitral valve repair and replacement are 1.4% and 6.0%, respectively (2005 STS database). It is significantly higher for patients undergoing concomitant CABG—7.2% for repair and 10.8% for replacement. In a recent study from the Northern New England Cardiovascular Disease Study Group, 10 variables were identified as independent predictors of in-hospital mortality: female sex, older age, diabetes, coronary artery disease, prior cerebrovascular accident, elevated creatinine, NYHA class IV, CHF, acuity, and valve replacement.[79,80] Ventricular function, prior cardiac surgery, and pulmonary hypertension have also been found to increase operative risk. Enriquez-Sarano and colleagues[81] have documented improved preservation of ventricular function with mitral valve repair relative to replacement.

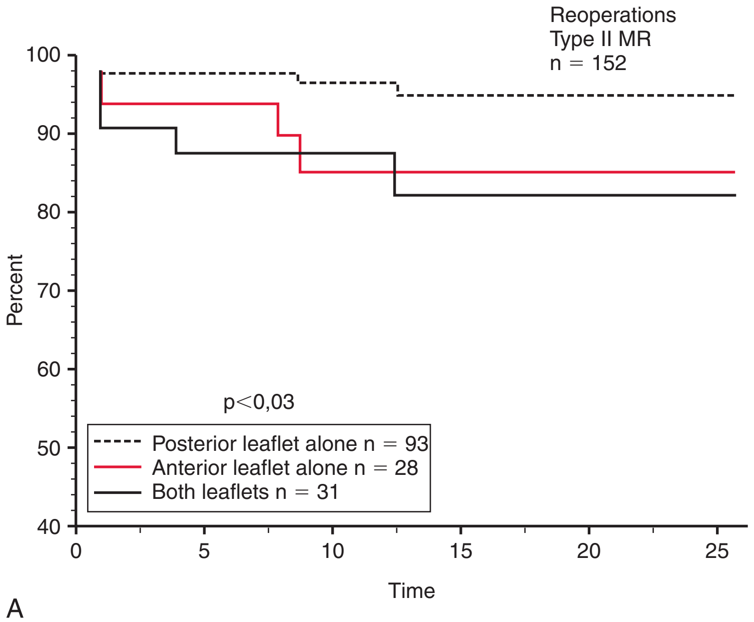
The incidence of major morbidity in most mitral valve surgeries remains low. The overall risk of stroke has been reported to be 2% to 3%. Deep sternal wound infections and reoperation for bleeding occur at similar rates to other valve surgery at 2% to 5%. Mitral valve surgery is a significant risk factor for postoperative atrial fibrillation with overall rates of approximately 50%. The incidence of heart block requiring permanent pacemaker insertion is about 3%.[82]

Late

The late outcomes of mitral valve surgery depend to a large degree on the underlying etiology of the mitral valve disease and whether a valve repair or replacement is performed. Long-term survival in generally healthy patients undergoing mitral valve repair for degenerative valve disease approaches that of an age-matched population. Several studies have documented improved long-term survival with valve repair, at least for degenerative and rheumatic etiologies. Moss et al[83] recently used propensity score methods to show improved late survival (RR = 0.52) with mitral valve repair relative to replacement. Late survival is decreased with ischemic compared with nonischemic etiologies. Additional predictors of late survival include ventricular function, NYHA functional status, age, and concomitant coronary artery disease. The leading causes of late death include heart failure, thromboembolism, stroke, endocarditis, anticoagulation–related hemorrhage, and myocardial infarction. Late functional status following mitral valve surgery is good with most studies reporting 90% of patients in NYHA class I-II.

The durability of mitral valve repair is most directly related to the etiology of the disease. The long-term results for repair of degenerative valves is excellent (Fig. 47–8). Carpentier's group reported their 20-year results.[84] The overall linearized rate of reoperation was 0.4% per year. Freedom from reoperation was 97% for patients with isolated posterior leaflet prolapse, whereas it was 86% and 83% for those with anterior or bileaflet prolapse, respectively. The results for repair of rheumatic valves, even at experienced centers, are not as good. Carpentier's group reported linearized rates of reoperation of 1.9% to 2.7% and 20-year freedom of reoperation of 46% to 65% depending on whether the initial dysfunction was type II (leaflet prolapse) or type III (leaflet restriction).[85]

As with aortic valve replacement, the long-term freedom from reoperation following mitral valve replacement is a func-



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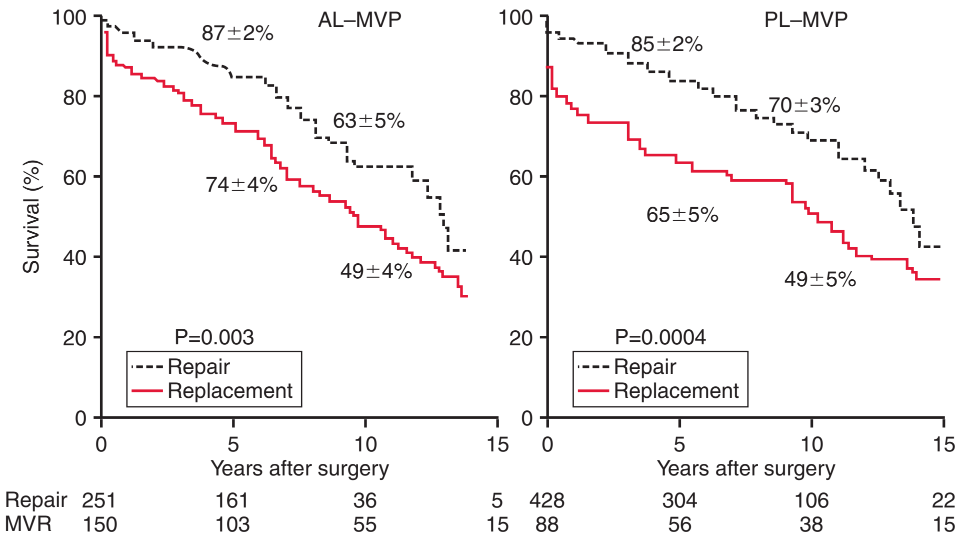


B

Figure 47–8 Long-term outcomes following mitral valve surgery for degenerative disease. **A,** Freedom from reoperation following mitral valve repair for type 2 MR, Carpentier's experience.[76] **B,** Long-term survival following mitral valve repair or replacement following mitral valve repair (MVP) for anterior leaflet (AL) and posterior leaflet (PL) disease, Mayo Clinic experience. (From Mohty et al: Circulation 2001;104:I-1).

tion of the prosthesis type and age. Although structural valve degeneration (SVD) of current generation mechanical valves is vanishingly rare, it is important to remember that the reoperation rate is not zero. Linearized rates of reoperation for prosthetic valve endocarditis, pannus overgrowth, and thrombosis are about 1% per year. Durability of bioprostheses in the mitral position, although improving, is not as good as in the aortic position, presumably because bioprostheses are exposed to greater forces during systole.[86,87] Durability remains excellent in elderly patients. Ten-year freedom from SVD for the Carpentier-Edwards pericardial valve was 100% in patients 70 and older. Performance in younger patients (60 and younger) is significantly worse with 60% to 80% freedom from SVD rates at 8 to 10 years,[86,88] highlighting the importance of achieving high rates of valve repair in these patients.

TRICUSPID VALVE SURGERY

Overview

Because most tricuspid valve dysfunction is a result of left heart lesions, isolated tricuspid valve surgery is relatively rare. Causes of isolated tricuspid disease requiring surgical correction included congenital anomalies (e.g., Ebstein's anomaly); RV dilatation from primary pulmonary hypertension; trauma (e.g., following endomyocardial biopsies); and endocarditis. Most tricuspid valve surgery is performed in conjunction with other valve surgery, usually mitral valve or replacement. Interest in tricuspid valve surgery has increased in recent years,[89,90] and the number of tricuspid valve operations in the STS database has increased significantly.

Indications

The indications for tricuspid valve surgery vary depending on whether the disease is primary or secondary. The data supporting these indications are not as well established as they are for aortic and mitral valve disease. Tricuspid stenosis is almost always rheumatic and rarely isolated, usually presenting with concomitant mitral valve disease. Severe symptomatic TR is considered a class IIA indication for isolated tricuspid valve surgery. The threshold for correcting TR at the time of other valve surgery has fallen in recent years. In the past even moderate degrees of TR were left alone with the assumption that correction of the left-sided lesions would decrease the pulmonary artery pressures and the degree of TR. Recent data, however, suggest that this does not reliably occur and most patients with moderate TR will undergo concomitant tricuspid annuloplasty. A recent report by Dreyfus et al[90] suggested that annular circumference alone, even in the absence of significant TR, should trigger concomitant annuloplasty.

Surgical Techniques

Approach

Most tricuspid valve surgery occurs in the context of multivalve surgery and thus is performed though a median sternotomy. Cannulation for cardiopulmonary bypass is usually performed in the ascending aorta and vena cavae, which are occluded below the cannulae to isolate the right atrium before atriotomy. The procedure can be performed under full cardioplegic arrest; under fibrillatory arrest; or on a beating heart under CPB, usually during rewarming.

Valve Repair

Most patients with TR will have type I or IIIB dysfunction without leaflet pathology (so-called "functional TR") and can be successfully treated with an annuloplasty alone. Commissuroplasty techniques, such as bicuspidization (obliterating the posterior leaflet), have largely been abandoned. Suture annuloplasty techniques, such as the DeVega annuloplasty, have been popular because they can be rapidly performed. Recent data, however, suggest that a formal prosthetic remodeling ring annuloplasty is superior to other techniques and should be the procedure of choice.[89]

Tricuspid valve repair of type II and IIIA dysfunction is rarely performed. Patients with Ebstein's anomaly can undergo successful repair using techniques developed by Carpentier and others. Those with degenerative changes or localized damage from trauma or endocarditis can undergo localized leaflet resection and reconstruction using techniques analogous to mitral valve repair.

Valve Replacement

Patients undergoing tricuspid valve replacement usually have extensive leaflet damage (rheumatic disease, endocarditis, biopsy trauma) or have failed prior valve repairs. The tradeoffs between tissue and mechanical valves are similar to valves in other positions, but there are fewer data. In the past, surgeons tended to avoid mechanical valves because of reports of high thrombosis rates secondary to low flow velocities. More recent data with bileaflet valves, however, are significantly better.[91,92] Although the rates of structural valve degeneration for bioprostheses in the tricuspid position appear to be lower than in the mitral position, the incidence of nonstructural degeneration, primarily pannus formation, appears to be higher, presumably as a result of organized thrombotic material. Most patients undergoing tricuspid valve replacement have limited life expectancy as a result of age or underlying disease and will therefore receive a bioprosthesis. Mechanical valves are generally reserved for younger, healthier patients and those who have or require another mechanical valve.

The techniques of implantation are similar to mitral valve replacement. Sutures along the septal leaflet must be taken superficially to avoid injury to the conduction system in the triangle of Koch. Patients undergoing mechanical valve implantation will usually have a permanent epicardial pacing lead placed in the operating room.

Results

Operative mortality rates following isolated tricuspid valve surgery are generally high (10% to 25%) because many of these patients have complex medical conditions and advanced right heart disease. Data on the additional risk of concomitant tricuspid valve repair in patients undergoing mitral valve surgery are limited. The operative mortality rate does appear to be higher but is probably due to the fact that the presence of TR is a marker for more advanced cardiopulmonary disease

than the impact of the tricuspid surgery itself. The main early morbidity is complete heart block requiring pacemaker insertion.

SPECIAL CONSIDERATIONS

Multiple Valve

Many patients presenting for heart valve surgery have multiple valve dysfunctions. Occasionally, two or more primary valve dysfunctions coexist and are both of sufficient severity to mandate surgery (such as in advanced rheumatic heart disease). More frequently, however, when valve dysfunctions coexist, it is usually possible to identify a primary dysfunction (which mandates surgery) and secondary dysfunctions (which arise from or coexist with the primary dysfunction). When the primary dysfunction is of the aortic valve, then secondary atrioventricular valve regurgitation may be a direct result of aortic valve disease and could resolve with isolated correction of the aortic lesion. In some patients, however, the secondary process is unrelated or may be so advanced that surgical correction of the aortic lesion alone will not suffice. Atrioventricular valve dysfunction as a primary lesion does not result in secondary aortic valve disease—the aortic valve disease in such cases is treated on its own merit.

Mitral and Tricuspid Disease

Tricuspid valve regurgitation often coexists in patients with mitral valve disease presenting for surgery. Traditionally such regurgitation was left uncorrected because it was assumed to be "functional" and that correction of mitral regurgitation results in resolution of tricuspid regurgitation. However, recent studies have challenged this thinking and evidence suggests that patients left with uncorrected tricuspid disease fare less well after surgery in terms of long-term symptoms and survival. Patients who initially have absent or mild/moderate tricuspid regurgitation at the time of mitral surgery also go on to develop worsening tricuspid regurgitation in the follow-up period.[90,93] Patients who do not have tricuspid repair at the time of surgery have a greater incidence of significant tricuspid regurgitation and higher incidence of congestive heart failure on long-term follow-up.[94,95] Mortality is high for reoperations performed to fix tricuspid regurgitation (up to 30%).[89]

Aortic and Mitral Disease

Patients with primary aortic valve disease will sometimes have secondary mitral valve disease. In patients with rheumatic disease, concomitant mitral valve repair or replacement is indicated if there is moderate mitral regurgitation or stenosis. In patients with degenerative AS, secondary mitral regurgitation is not uncommon, presumably as a result of left ventricular dilatation and pressure overload. Mitral valve repair is certainly indicated if the MR is severe. Most mild to moderate MR, however, is left alone because the data for intervening at this threshold is mixed.[96-99] In the past, some have argued that patients undergoing concomitant aortic and mitral valve surgery should receive a second prosthesis instead of a mitral valve repair. Given the current results of mitral valve repair, this does not appear justified and every effort should be made to repair the mitral valve in this setting. Gillinov et al[100] have documented improved survival with this approach.

Reoperation

The success and improved long-term outcomes of cardiac surgery in the 1980s and 1990s have resulted in millions of surviving patients worldwide who have had previous cardiac surgery. As these patients age, a proportion will require reoperative valve surgery for valve-related complications or for progression of native valve disease.

Valve surgery in the reoperative setting is more complex compared with first-time surgery because of pericardial adhesions, patent bypass grafts, often advanced cardiac dysfunction with pulmonary hypertension, and technical issues relating to re-replacing heart valves. The mortality risk is higher than for first-time surgery, although this risk has fallen in recent years, with some centers reporting mortality rates below 5%.

The indications for surgery differ slightly in the reoperative setting because the risk of operative mortality may outweigh the benefits if conventional indications (as for first time surgery) are applied. The major consideration in deciding to offer valve reoperation is the relief of symptoms rather than prolongation of life expectancy. In some instances reoperative surgery is undertaken for survival benefit, such as in young patients with structural valve degeneration and in patients in whom the valve disease would otherwise be fatal (such as endocarditis).

Patients requiring reoperations present unique surgical challenges. These patients are often managed medically until the disease is advanced, and surgery is only undertaken when there are no nonsurgical options. Subsequently, many patients are severely compromised, debilitated with poor functional state, have poor LV function, or are old with comorbidities. These patients must have a detailed preoperative work-up because even small lapses can precipitate major catastrophe. Cardiac catheterization is performed to delineate coronary anatomy and measure pulmonary pressures. CT is useful in defining the relationships of the cardiac chambers and great vessels to the sternum; sometimes sternal re-entry may be considered so hazardous that alternative surgical approaches are required. Thorough echocardiographic assessment of all heart valves is necessary because many patients will have multiple valve dysfunctions. Details of the prior cardiac operations are obtained because previous difficulties, observations, or complications may be relevant to the planned procedure. Screening for peripheral vascular disease is necessary in older patients because cannulation of peripheral vessels for cardiopulmonary bypass may be required and is occasionally life saving.

Principles of surgical repair or replacement are similar to that for primary valve surgery. When valves are repairable, this remains the treatment of choice. A failed prior valve repair does not mandate a valve replacement if the valve is easily repairable. If valve replacement is required, then choice of prosthesis should take into account the balance between the risks of anticoagulation and the probability and risks of another future reoperation (for biologic valve degeneration). Sometimes the surgeon may choose to re-replace a normal-functioning prosthetic valve so that the patient can stop anticoagulation (replace mechanical with bioprostheses) or to

avert inevitable future structural valve degeneration (such as a patient with a 10-year-old functioning porcine valve requiring another cardiac procedure).

Endocarditis

Although medical management remains the cornerstone of therapy for most bacterial endocarditis, surgery has a critical and life-saving role in the treatment of complicated cases. A detailed discussion of the surgical management of patients with endocarditis is beyond the scope of this chapter.

Diagnosis is usually based on characteristic lesions seen on echocardiography, with or without positive blood cultures (see Chapter 44). Transesophageal echocardiography is the most sensitive and specific investigation for defining endocarditis lesions and is performed on most cases of endocarditis to evaluate for indications for surgery. Once there is an indication for surgery, operation is generally undertaken within 24 hours because delay is associated with increased morbidity and mortality. One exception is if there has been an embolic stroke, in which case early surgery carries a higher risk of hemorrhagic extension of the stroke.

The principles of surgical treatment are débridement of all infected tissues, drainage of abscesses, and correction of hemodynamic dysfunction. Following débridement, the valve annulus (if affected) is reconstructed and the valve is repaired when feasible or replaced. Abscesses of the aortic root will usually necessitate root replacement. Choice of valve prosthesis usually depends on surgeon preference. Allografts and autografts are more resistant to infection, but with thorough débridement and continuation of antibiotic therapy, reinfection of the newly implanted valve is uncommon regardless of the type of prosthesis used.

Ischemic Heart Disease

Ischemic and valvular heart diseases frequently coexist, making surgical decision-making and management more complex. Although a patient with advanced disease can certainly present with both ischemia and congestive heart failure, in most patients one disease will dominate the presentation and the other is more incidental. The management depends on which disease dominates the clinical picture.

Incidental Coronary Disease in Valve Surgery Patients

Patients with risk factors for coronary artery disease (including age) requiring heart valve surgery generally undergo preoperative screening angiography. The presence of concurrent coronary artery disease reduces survival after heart valve surgery.[101] Furthermore, the presence of coronary artery disease can lead to patchy distribution of cardioplegic solution, complicating myocardial preservation. The subendocardial region is most vulnerable to poor protection and intraoperative ischemic injury in the presence of coronary disease, particularly in the setting of LV hypertrophy. In patients with poor ventricular function, incidental coronary artery disease may contribute to the poor ventricular function—MRI is useful in this setting to identify ischemic or infarcted myocardium and define potential utility of bypass grafting.

Most surgeons would perform concurrent coronary artery bypass at the time of heart valve surgery when there are critical coronary lesions (>70% stenosis in a proximal coronary artery or >50% in the left main coronary artery). Surgery classically consists of an internal mammary artery graft to the left anterior descending artery and venous conduits for other vessels. Although concurrent coronary artery bypass surgery is associated with higher perioperative mortality compared with isolated valve surgery, there is no evidence that this is related to the additional surgical procedure per se. Higher mortality is probably a reflection of the increased risk of valve surgery when there is concurrent ischemic heart disease. If critical coronary lesions are not bypassed, the patient is at greater risk of perioperative myocardial infarction.

Staged procedures with percutaneous coronary revascularization (PCI) followed by valve surgery is an alternative strategy for handling concurrent coronary artery disease. Revascularization before surgery allows for an expeditious valve operation with shorter ischemic and cardiopulmonary bypass times. The timing of PCI relative to valve surgery and management of antiplatelet therapy are important considerations with this approach.

Incidental Valve Disease in Coronary Surgery Patients

Widespread use of echocardiography in the work-up of cardiovascular disease has led to increased diagnosis of incidental valvular pathology in patients undergoing nonvalvular heart surgery, particularly coronary surgery. If the valve disease is truly incidental, then the patients are asymptomatic by definition. The indications for valve surgery in any asymptomatic valve patient (see earlier discussion) also apply in the patient having coronary artery bypass surgery. For example, severe AS and severe mitral regurgitation will require surgical correction.

Patients undergoing coronary bypass surgery who have valve lesions that do not warrant surgery on their own merit pose a diagnostic dilemma. These include patients with moderate degrees of valve regurgitation or stenosis. In these patients a balance must be made between the risks of concurrent valve surgery and the anticipated rate of disease progression if the valve were left untreated and the likelihood and implications of future reoperation. Untreated disease may progress such that the patient requires future reoperation at higher risk. Another important consideration is whether the valve is repairable or whether it requires replacement. The threshold for intervention may be lower in patients with repairable valves, but when a valve with moderate dysfunction is irreparable, decisions to do valve replacement should be taken seriously because a moderately diseased native valve is replaced by a prosthetic valve, which is at risk of prosthesis-related disease. Age also plays a role—younger patients are generally treated more aggressively with moderate lesions often ignored in elderly patients.

Aortic Stenosis in Coronary Artery Bypass Grafting Patients

AS is the most frequently diagnosed incidental valve disease. Elderly patients undergoing coronary artery bypass not infrequently have coexisting mild to moderate AS. Review of

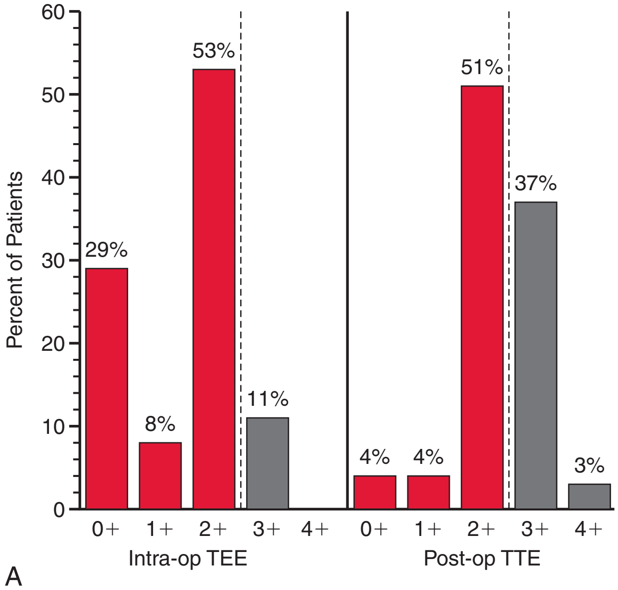
the literature shows that AS gradient progresses at a rate of 5 to 10 mm Hg per year, and the valve area decreases by about 0.1 cm^2 per year.[39] Therefore young patients and older patients who have a life expectancy more than 5 years should be offered concurrent aortic valve replacement for moderate stenosis because future symptomatic AS is likely.[36]

Whereas concurrent aortic valve replacement in this setting does not substantially increase mortality, reoperative surgery for aortic valve replacement in the presence of patent coronary grafts has traditionally carried significant risk. Observation of significant valve calcification or severely restricted leaflet motion on TEE is also an indicator of aggressive disease and requires concurrent valve replacement. Mild AS (gradient < 25 mm Hg) does not require treatment.

Mitral Regurgitation in Coronary Artery Bypass Grafting Patients

Although unsuspected degenerative or rheumatic MR can occasionally be seen in patients undergoing CABG, in the vast majority of patients with MR at the time of CABG the underlying etiology will be ischemic. Our understanding of ischemic MR has improved dramatically over the past decade. The mechanism is complex but fundamentally results from displacement of the papillary muscles resulting in leaflet tethering and restricted leaflet motion (type IIIB dysfunction).

Severe ischemic MR has always been considered an indication for concomitant mitral valve surgery. The management of moderate ischemic MR, however, has been more controversial. Data from the early 1990s suggested that moderate ischemic MR could be ignored at the time of CABG.[102] More recent data, however, overwhelmingly support concomitant valve repair for moderate (3+) ischemic MR in most patients. Our group has shown that CABG alone does not reliably correct moderate MR with 90% of patients left with 2+ MR or greater (Fig. 47–9A).[103] This and other studies have also documented marked intraoperative downgrading of ischemic MR. The decision to intervene should therefore be based on a preoperative transthoracic echo. We have also shown that concomitant mitral annuloplasty can be performed with an operative risk of < 4%.[104] Patients with 2-3+ MR are particularly challenging, especially if they are elderly and have comorbidities that increase the risk of concomitant mitral valve surgery. Considering factors that indicate the ischemic MR is chronic and physiologically significant, such as ventricular function, atrial fibrillation, left atrial dilatation, and intraoperative provocative testing is important and may be useful in equivocal cases (see Fig. 47–9B).[105]



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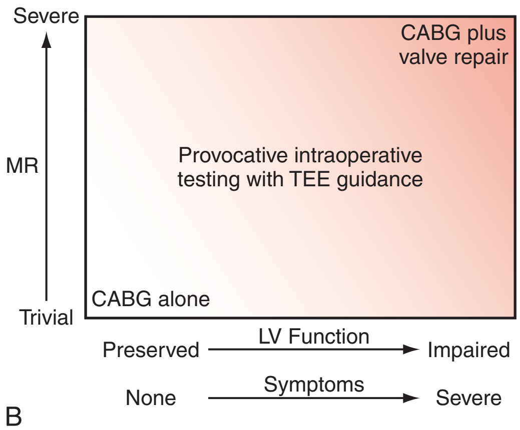

B

Figure 47–9 Ischemic mitral regurgitation at the time of CABG. **A,** Data showing that CABG alone does not correct moderate ischemic MR and intraoperative TEE downgrades ischemic MR. All patients had 3+ preoperative MR and underwent CABG alone.[103] **B,** Decision-making in ischemic MR at the time of CABG.[105]

Atrial Fibrillation

Surgical treatment of atrial fibrillation is based on the Maze operation, which was developed by Cox in the 1980s.[106] The operation is reported to be effective in curing atrial fibrillation in 80% to 90% of patients and involves making encircling incisions around the venous atrial inflows to stop the propagation of abnormal atrial impulses (which usually originate around these veins) (see Chapter 22). The classic Maze procedure, however, involved making a complex network of atrial incisions, which prolonged the operation and were associated with increased morbidity; for this reason, the Maze operation, despite its effectiveness, was not widely adopted by surgeons.

A recent resurgence of interest in atrial fibrillation surgery has occurred, however, because of the availability of technology that allows surgeons to easily perform ablation around the pulmonary veins without the added complexity and morbidity associated with the original “cut and sew” operation. With several commercially available energy sources (e.g., radiofrequency, cryotherapy, laser, microwave, ultrasound) and devices, the surgeon can create transmural lesions in the atria without making surgical incisions. These transmural lesions have been shown to be as effective as the original “cut and sew” lesions. Although the focus is primarily on pulmonary vein isolation, the surgeon can also create additional left and right atrial lesions to mimic a complete Maze operation (which may improve the efficacy compared with pulmonary vein isolation alone). Using the commercially available probes and clamps, ablation for atrial fibrillation can be undertaken epicardially before the surgeon commences cardiopulmonary bypass or endocardially with the atrium

open for the mitral repair. Modern devices are relatively simple to apply, do not require much specialized surgical skill, and do not unduly prolong the operation. Concurrent atrial fibrillation surgery is now the standard of care for patients undergoing heart valve surgery who have a prior history of atrial fibrillation. The left atrial appendage is often excised or oversewn at the time of mitral valve surgery.

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Treatment of Cardiovascular Manifestations of HIV

Priscilla Y. Hsue and David D. Waters

CHAPTER CONTENTS

In 2004 an estimated 40 million people were living with HIV, and 5 million people were newly infected.[1] Since the introduction of highly active antiretroviral therapy (HAART) in the mid- to late 1990s, the rates of HIV-associated morbidity and mortality have been dramatically reduced.[2] In the HIV Outpatient Study, the mortality rate in 1255 patients in the United States with at least one CD4+ count below 100 cells/mm^3 declined from 29.4 to 8.8 per 100 patient-years from 1995 to the second quarter of 1997,[2] a time period that coincided with the initiation of protease inhibitors. Similarly, in a European cohort study of 4270 patients who had had a CD4+ count below 500 cells/mm^3, the mortality rate fell from 23.3 to 4.1 per 100 patient-years during mid-1995 and late 1997 to early 1998.[3] The decrease in mortality rates in these studies was accompanied by a decline in the incidence of opportunistic infections[2] and correlated with the intensity of antiretroviral therapy.[3]

However, with new medications and patients living longer, a new set of cardiovascular issues including atherosclerosis and metabolic abnormalities, such as hyperlipidemia, hypertension, and hyperglycemia, have appeared. Herein we review the different cardiovascular complications associated with HIV and discuss their treatment.

ANTIRETROVIRAL THERAPY

Current guidelines recommend that all patients with symptomatic HIV disease and asymptomatic patients with ≤ 200 CD4 cells/μL should be placed on antiretroviral therapy.[4] In asymptomatic patients with > 200 but ≤ 350 CD4 cells/μL, antiretroviral treatment should be considered.[4] Currently, HAART consists of four classes of drugs: nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and a cell membrane fusion inhibitor. Initial regimens usually consist of three drugs: two NRTIs combined with either an NNRTI or a PI.[4] The superiority of different treatment regimens compared with others is still being studied.[4]

PROTEASE INHIBITORS

Protease inhibitors are the most widely used class of antiretroviral agents used to treat HIV and are listed in Table 48–1 along with important drug–drug interactions and side effects.[5] PIs are also associated with a plethora of side effects including disorders of glucose and lipid metabolism, hepatotoxicity, gastrointestinal complaints, sexual dysfunction, and an increased risk of bleeding.[6] These symptoms are frequently severe enough to cause discontinuation of therapy.[7]

In addition, because all PIs inhibit metabolism of the cytochrome P450 3A4 enzyme, they interact with many cardiac medications, as shown in Table 48–1. Case reports of rhabdomyolysis have been reported with the combination of a PI and a statin[6,8]; in one patient, nelfinavir and simvastatin caused death due to severe rhabdomyolysis.[9] Simvastatin should not be used in patients who take PIs, and the dose of atorvastatin should be reduced. Because it is not metabolized by the cytochrome P450 system, pravastatin appears to be safe.

NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

NRTIs are structurally defective analogues of viral nucleotides, and, after being incorporated into viral DNA, they prematurely terminate viral strand synthesis and inhibit viral replication. Unlike PIs, NRTIs are generally well tolerated and do not inhibit the cytochrome P450 system; however, they

Table 48–1 Protease Inhibitors

Generic Name	Typical Dose*	Pills/Day	Common Adverse Events	Important Drug Interactions†
Amprenavir	1200 mg bid	16	Lactic acidosis, periorbital and peripheral numbness, rash, nausea, diarrhea	Lovastatin, simvastatin, bepridil
Atazanavir	400 mg/day	2	Lactic acidosis, hyperbilirubinemia, ↑ PR interval	Proton pump inhibitors, bepridil
Fosamprenavir	1400 mg bid	4	Prodrug of amprenavir with higher bioavailability	Flecainide, propafenone, lovastatin, simvastatin
Indinavir	800 mg tid	6	Dry eyes, mouth and skin, nephrolithiasis, hyperbilirubinemia, neutropenia, paronychia, vasculitis	See † below
Lopinavir/Ritonavir	400/100 mg bid	6	Pancreatitis, GI side effects common but mild	See ritonavir and † below
Nelfinavir	1250 mg bid or 750 mg tid	9-10	Nephrolithiasis, more diarrhea than other PIs	Amiodarone quinidine, lovastatin, simvastatin, ?atorvastatin
Ritonavir	600 mg bid	12	Pancreatitis, altered taste sensation	As for nelfinavir; bepridil, clozapine, estradiol, flecainide, methadone, propafenone
Saquinavir	1200 mg tid	18	Altered sense of taste	See † below

*The typical dose may not be the dose used with combination therapy.
†All PIs interact with antiarrhythmic drugs, ergots, triazolobenzodiazepines (alprazolam [Xanax], midazolam [Versed], triazolam [Halcion]), and pan-inducers of the cytochrome P450 enzymes (barbiturates, carbamazepine, ethanol, phenytoin, and rifamycins). These drugs should not be used with PIs.
PI, protease inhibitor.

do cause mitochondrial toxicity, which is expressed clinically as peripheral neuropathy, myopathy, lactic acidosis, hepatic steatosis, pancreatitis, and lipodystrophy (Table 48–2).[10]

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

NNRTIs block DNA elongation by directly binding to the reverse transcriptase enzyme.[10,11] The antiviral potency and good tolerability of NNRTIs make them a favored component of HAART regimens, particularly because toxicity and viral cross-resistance do not overlap with NRTIs. Their most frequently reported side effects are rash, elevation of liver enzymes, and fat redistribution (see Table 48–2).[10,11]

Enfuvirtide is one of the newest classes of antiretroviral drugs, entitled *fusion inhibitors*.[12] This medication prevents conformational changes that are necessary for the fusion of virions to host cells. Because this drug is costly and requires administration by injection, enfuvirtide is generally reserved for patients who have failed other antiretroviral regimens.

METABOLIC EFFECTS OF HIV INFECTION AND ANTIRETROVIRAL THERAPY

HIV disease and antiretroviral therapy have been associated with many different metabolic effects including hyperlipidemia, insulin resistance, and hypertension. However, the relationships among HIV infection, antiretroviral therapy, and cardiac risk factors remain poorly understood and complex. In untreated HIV patients, lower CD4 counts are associated with lower total blood cholesterol, lower HDL-cholesterol, and higher triglyceride levels.[13] Independent of changes in body composition, PIs induce hyperlipidemia and insulin resistance in HIV patients.[14] Different PIs appear to have differing effects on lipid metabolism. For example, ritonavir raises triglycerides and lowers HDL-cholesterol slightly, with no effect on LDL-cholesterol.[15,16] Indinavir has no effect on lipoproteins but causes insulin resistance,[17] whereas amprenavir does not affect lipoproteins.[16] Lopinavir/ritonavir increases triglycerides but has no effect on LDL or HDL-cholesterol or on insulin resistance.[18] These studies involved HIV-negative subjects to isolate the effects of the drugs and were short in duration.

The Multicenter AIDS Cohort Study included HIV-infected patients treated for longer periods of time; the results of this study help to provide a clearer picture of lipid changes associated with HIV disease and treatment.[19] Fifty HIV patients in this study had blood samples available from before they became HIV positive, from before HAART was initiated at a mean of 7.8 years later, and at 4 follow-up visits during treatment. As shown in Figure 48–1, total and LDL-cholesterol decreased after the onset of HIV disease but returned to preinfection levels or higher with HAART. However, HDL-cholesterol levels decreased markedly after the onset of HIV

Table 48–2 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Generic Name	Typical Dose	Common Adverse Events
NRTIs		
Abacavir (ABC)	300 mg bid	Hypersensitivity reaction in about 4%
Didanosine (ddI)	250 mg/day if <60 Kg 400 mg/day if ≥60 Kg	Peripheral neuropathy in 15%, optic neuritis, rare pancreatitis
Emtricitabine	200 mg/day	Stopping may exacerbate hepatitis B
Lamivudine (3TC)	150 mg bid	Generally well tolerated
Stavudine (d4T)	30 mg/bid if < 60 Kg 40 mg/bid if ≥ 60 Kg	Peripheral neuropathy—higher risk in patients with CD4 counts < 50
Tenofovir	300 mg/day	Nausea; generally well tolerated
Zalcitabine (ddC)	0.375-0.75 mg tid	High rate of peripheral neuropathy, oral ulcers; rarely used due to toxicity
Zidovudine (AZT)	300 mg bid	Nausea, headache, fatigue, anemia, neutropenia, neuropathy, myopathy
Combination NRTIs		
AZT + 3TC	1 tab bid	Same as AZT
AZT + 3TC +ABC	1 tab bid	Same as AZT and ABC
NNRTIs		
Delavirdine	400 mg tid	Rash, fat redistribution, ↑ ALT/AST
Efavirenz	600 mg/day	Rash, CNS symptoms including insomnia
Nevirapine	200 → 400 mg/day	Rash, hepatitis

CNS, central nervous system; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside analogue reverse transcriptase inhibitor.

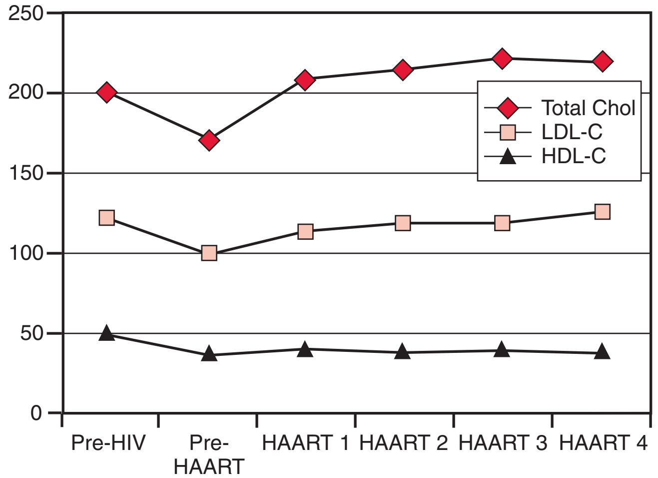

Figure 48–1 This figure shows lipid levels in HIV-infected men before HIV seroconversion (pre-HIV), before starting HAART (pre-HAART), first visit after starting HAART (HAART 1), second visit after HAART (HAART 2), third visit after HAART (HAART 3), and fourth visit after HAART (HAART 4). The mean interval between the pre-HIV measurement and the pre-HAART measurement was 7.8 years and between pre-HAART and the first post-HAART measurement 1.3 years; the subsequent mean intervals between measurements were 0.5, 2.1, and 0.6 years. Total and LDL-cholesterol levels increased during HAART but were depressed before treatment compared with the values before HIV infection. (From Riddler SA, Smit E, Cole SR, et al: Impact of HIV infection and HAART on serum lipids in men. JAMA 2003;289:2978-82.)

and did not recover. Triglycerides were measured once during treatment and were elevated at 225 mg/dL.

A summary of the effects of PIs on lipids in HIV patients showed that these drugs increase total and LDL-cholesterol by 20% to 60% and may more than double triglyceride levels.[20] Replacement of a PI with an alternative class of medication including NNRTI, such as nevirapine, efavirenz, or an NRTI like abacavir, has been shown to reduce LDL-cholesterol and triglyceride levels and to increase HDL-cholesterol.[21]

Hypertension has been reported in up to one third of HIV patients.[22,23] In some studies NNRTIs or PIs have been linked to hypertension,[24,25] although other studies show no association.[22] The hypertension associated with HIV appears to be linked to insulin resistance and the metabolic syndrome.[23]

LIPODYSTROPHY AND THE METABOLIC SYNDROME

HIV-associated fat redistribution, also called *lipodystrophy* or *lipoatrophy*, is characterized by a selective loss of fat from the face and extremities but can also be associated with an accumulation of fat in the neck, dorsocervical region, abdomen, and trunk.[21,26] Lipodystrophy in HIV patients is associated with metabolic abnormalities, such as insulin resistance, impaired glucose tolerance, elevated triglycerides, low HDL-cholesterol, and hypertension.[27,28]

Lipodystrophy becomes clinically evident in 20% to 35% of patients after 1 to 2 years of combination HAART.[29] The type and duration of antiretroviral therapy is strongly associated with the development and severity of lipodystrophy.

Combination therapy with a PI and two NRTIs, particularly stavudine with didanosine, is most likely to induce severe lipodystrophy.[21] Exercise training, either alone[30] or with metformin,[31] has been reported to improve body composition in patients with lipodystrophy. Injection of synthetic fillers has been reported to improve cosmetic appearances in HIV patients.[32]

SURROGATE MEASURES OF ATHEROSCLEROSIS IN HIV PATIENTS

The use of PIs in HIV-infected adults is associated with endothelial dysfunction as assessed by brachial artery flow-mediated vasodilation, which appears to be mediated by the atherogenic dyslipidemia induced by PIs.[33] Carotid B-mode ultrasound has been used to assess subclinical atherosclerosis in HIV patients.[34-39] In a study of 423 HIV-infected patients, conventional risk factors but not lipodystrophy or HAART were independent predictors of increased carotid IMT.[38]

At San Francisco General Hospital, mean carotid IMT in 148 HIV-infected adults was thicker than in age- and sex-matched controls ($P < 0.001$).[39] At 1-year follow-up, HIV patients had rapid progression of carotid IMT compared with controls ($P = 0.002$). Carotid IMT thickness correlated with classic risk factors, but progression of carotid IMT also correlated with a low nadir CD4 count.

HIV INFECTION AND MYOCARDIAL INFARCTION

The first cases of coronary disease in two young HIV-infected men who received PIs were reported in 1998. Presently, controversy still exists as to whether the rate of coronary events is increased in HIV patients and whether or not this increase is mediated by HAART.

A retrospective study of 36,766 HIV patients treated at Veterans Affairs facilities between 1993 and 2001 found no increase in cardiovascular or cerebrovascular events in patients who received HAART during a mean follow-up period of 40 months.[40] Similarly, in a meta-analysis of 30 randomized clinical trials, the incidence of myocardial infarction (MI) was not higher in patients receiving PIs compared with NRTIs; however, the duration of treatment was only one year and the number of events was small.[41]

However, in the HIV Outpatient Study (HOPS), the frequency of MI increased after the introduction of PIs ($P = 0.0125$) and MI occurred in 19 of 3247 patients taking PIs, but in only 2 of 2425 not taking PIs.[42] The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group was a prospective study of 23,468 HIV patients followed for a mean duration of 1.6 years, with an average exposure to antiretroviral therapy of 1.9 years.[43] The risk of MI increased with longer exposure to combination antiretroviral therapy with the adjusted relative risk per year of exposure of 1.26 (95% CI 1.12 to 1.41, $P < 0.001$).

In the French Hospital Database on HIV, MI was diagnosed in 60 of 34,976 patients during a median follow-up of 33 months.[44] In this study, patients taking PIs had a significantly higher risk of MI compared with patients not taking PIs, with a relative risk of 2.56; the relative risk for those taking PIs for > 30 months compared with < 18 months was 3.6 (95% CI 1.8 to 6.2). In the Kaiser Permanente Medical Care Program of Northern California database, 72 coronary events including 47 MIs were documented in 4159 HIV patients during a median follow-up of 4.1 years.[45] Median exposure time to PIs was 2.8 years. The coronary event rate was similar in patients taking and not taking PIs; however, HIV-infected patients had a rate of 6.5 compared with 3.8 events per 1000 patient-years in non-HIV controls ($P = 0.003$).

Although additional studies are necessary with longer-term follow-up, together these studies suggest that the rate of MI is higher in HIV patients who take PIs and that the risk increases as the duration of treatment lengthens. Traditional coronary risk factors usually exert their influence for decades before a coronary event occurs. Because an increase in risk can be detected after only a short exposure, the use of PIs may be associated with a period of high risk or may serve as potent stimuli for atherogenesis. The coronary event rates in these studies are relatively low but might be expected to increase as the HIV population ages.

CLINICAL FEATURES OF CORONARY DISEASE IN HIV PATIENTS

The clinical features of 334 patients, 225 (67%) of whom presented with acute MI, are tabulated from 7 reports and are shown in Table 48–3.[7,46-52] Only 31 (9%) of these patients were women. The average age of the patients with HIV and MI is

Table 48–3 Clinical Features of Coronary Disease in HIV Patients

Study	Patients (*n*)	Age (yr)	Current Smoking	CD4 Count (cells/mm^3)	PI Use	MI on Presentation	1 Vessel Disease
David et al[46]	16	43*	81%	234 (74-731)*	69%	8/16 (50%)	NA
Matetzky et al[47]	24	47 ± 9	58%	318 ± 210	71%	All MI	5/21 (24%)
Escaut et al[48]	17	46 ± 6	71%	272 ± 185	65%	11/17 (65%)	9/17 (53%)
Mehta et al[49]	129†	42 ± 10	NA	313 ± 209	NA	82/106 (77%)	26/76 (35%)
Ambrose et al[50]	51	48 ± 9	55%	426 ± 290	59%	34/51 (67%)	21/45 (47%)
Varriale et al[51]	29	46 ± 10	55%	>500 in 18/29	66%	All MI	NA
Hsue et al[52]	68	50 ± 8	68%	341 (3-4360)*	49%	37/68 (54%)	20/56 (36%)

*Median value; all other values are means.
†Patients drawn from 25 previous reports.
MI, myocardial infarction; NA, not reported; PI, protease inhibitor.

approximately 8 to 11 years younger than in HIV-negative patients with MI. The proportion of patients receiving PIs ranged from 49% to 71%. In each of these studies, more than half of the patients smoked cigarettes at the time of their coronary event.

Mean HDL-cholesterol levels were low in each of the 3 studies in which they were reported, ranging from 28 to 35 mg/dL.[47,48,52] These levels were significantly lower than those of HIV patients without coronary disease in the French cohort[48] and lower than non-HIV controls with coronary disease in the other two studies.[47,52] Mean LDL-cholesterol levels were lower in HIV coronary patients than in non-HIV coronary controls in one study[47] but not in another.[52] In the French cohort, LDL-cholesterol levels were much higher in the HIV patients with coronary disease than in those without.[48]

As expected in a younger population, single vessel disease is common,[47-50,52] and the TIMI risk score[53] is low if an acute coronary syndrome is present.[52] Thus, HIV-infected patients tend to have good outcomes after coronary events. Only 9 deaths (4.8%) occurred in hospital among 189 patients with follow-up reported among the studies included in Table 48–3.[47,48,50-52]

Coronary angioplasty or stenting has often been performed in these patients, and the immediate results have been excellent; however, the restenosis rate appears to be higher than that of patients without HIV infection.[47,52] In one study, restenosis developed in 15 of 29 HIV patients compared with 3 of 21 non-HIV controls (52% versus 14%, $P = 0.006$).[52] Similarly, in another study, 6 of 14 HIV patients had restenosis that required target vessel revascularization compared with 4 of 38 uninfected controls (43% versus 11%, $P = 0.02$).[47] Restenosis rates are higher after both balloon angioplasty and stenting. Thus because of higher restenosis rates, HIV patients should be considered for drug-eluting stents. To date, no studies have examined the utility of drug-eluting stents in this patient population.

In a small series of 37 HIV patients who were followed after coronary bypass surgery, event-free survival was 81% at 3 years.[54] Of note, the median age of the bypass patients in this study was only 44 years. There have been no large-scale studies of HIV patients who were referred for bypass grafting studying with long-term follow-up, and no studies have reported graft patency rates after coronary bypass in HIV patients.

TREATMENT OF CORONARY RISK FACTORS IN HIV PATIENTS

Currently, there is no direct evidence that treating risk factors for CAD in HIV patients improves outcomes; however, it appears reasonable to extrapolate from observations on the treatment of traditional risk factors in non-HIV patients.

Cigarette smoking is one of the most common and modifiable risk factors in patients with HIV infection; the prevalence of cigarette smoking in HIV patients has been reported to be as high as 70% to 80% in some areas,[55] and compared with other smokers, HIV patients are less likely to have contemplated quitting.[55] Different treatments that have been tested in pilot studies of HIV-infected smokers include interventions led by nurses[56] and the provision of cellular telephones to low-income, HIV-infected smokers in order to assist counseling.[57] Cigarette smoking is implicated in many of the other complications of HIV,[55] along with atherosclerosis and pulmonary disease, and it should be a major focus of attention by the physician in HIV patients.

The Adult AIDS Clinical Trials group recommends that dyslipidemia be managed according to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III.[58] However, HIV patients have several particular issues in dyslipidemia. All current PIs and all statins, except pravastatin, are metabolized by the cytochrome P450 system. In healthy volunteers the PI combination of ritonavir/saquinavir has been shown to increase the area under the curve (AUC) for 24-hour blood statin level by 30-fold for simvastatin and by 79% for atorvastatin, while the AUC decreased by 50% for pravastatin.[59] Simvastatin and lovastatin are contraindicated in patients taking PIs, and atorvastatin should be used cautiously.[58] Although pravastatin is safe, it has weaker LDL-cholesterol lowering effects. Ezetimibe, which works by inhibiting cholesterol absorption, has not been studied in HIV patients but may represent an attractive approach to LDL-cholesterol lowering because of its lack of drug–drug interactions. Atazanavir, one of the newer protease inhibitors, does not appear to be associated with lipid abnormalities,[60] and thus switching HIV patients to this drug represents an option for patients who have lipid levels that are difficult to manage. An algorithm for management of elevated LDL in HIV patients is shown in Figure 48–2.

NNRTIs also affect the P450 cytochrome 3A4 enzyme, but in different ways: delavirdine inhibits it and thus has the same implications with respect to statin use as PIs do.[58] Efavirenz is a mixed inducer and inhibitor of this enzyme, and little data are available to define how this NNRTI affects statin concentrations.[58]

Elevated triglycerides are common in HIV-infected patients. Fibrates (bezafibrate, fenofibrate, and gemfibrozil) appear to reduce triglycerides effectively in HIV patients who receive HAART[21,61]; however, fibrates are conjugated by glucuronidation with renal elimination. Ritonavir and nelfinavir

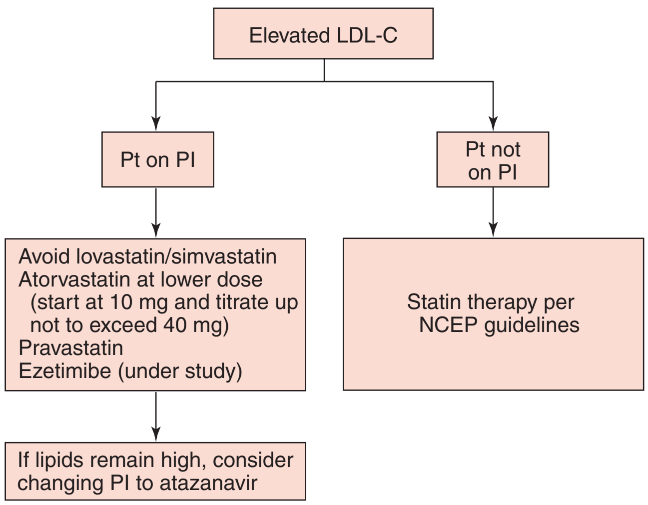

Figure 48–2 A suggested algorithm for management of elevated LDL cholesterol in HIV-infected patients. PI, protease inhibitor.

are known inducers of glucuronidation and thus could diminish the efficacy of fibrates.[58] If fibrates are prescribed in combination with statins, regular monitoring of CK levels is recommended because of the increased risk of myopathy. Niacin is an alternative choice to raise HDL levels and lower triglycerides but may be a poor choice for many HIV patients because of its propensity to worsen blood glucose levels. An algorithm for management of elevated triglycerides and low HDL cholesterol is shown in Figure 48–3.

Hypertriglyceridemia is often accompanied by other components of the metabolic syndrome: low HDL-cholesterol, increased remnant lipoproteins, small LDL particle size, abdominal obesity, hypertension, insulin resistance, and glucose intolerance (a proinflammatory state and a prothrombotic state).[62] The primary treatment target for the metabolic syndrome is obesity, and the recommended measures include diet and exercise.[63] Even modest reductions in body weight improve dyslipidemia, hypertension, and glucose intolerance, as well as levels of inflammatory and thrombotic markers.[63]

Similar to other patients with chronic infection, HIV patients have higher levels of hs-CRP compared with age- and sex-matched controls.[39] CRP was an independent predictor of 5-year mortality in one small study of HIV-infected women.[64] The anti-inflammatory effects of statins might thus contribute to any benefit these drugs might have in HIV patients, as they also might be beneficial in patients without HIV disease. Finally, as with HIV-uninfected patients, primary prevention of coronary disease in appropriate patients using aspirin therapy should be implemented.

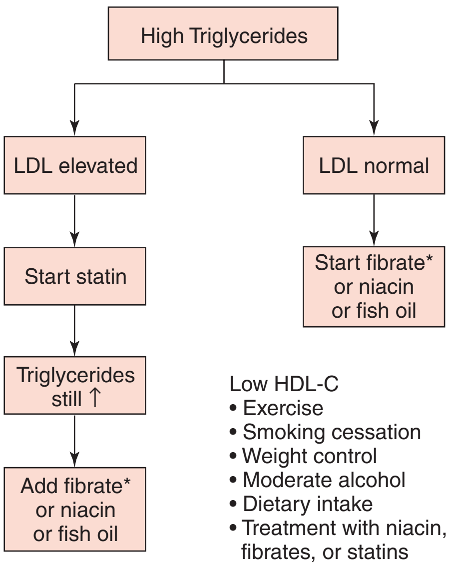

Figure 48–3 Algorithm for managing elevated triglycerides and low HDL-cholesterol in HIV-infected patients. *Caution is advised when considering the combination of fibrates and statins due to increased risk for myopathy. When used in combination with a statin, fenofibrate is preferred. The efficacy of fibrates is reduced in patients receiving Ritonavir or Nelfinovir.

MYOCARDIAL INVOLVEMENT IN HIV

The HIV virus has been recognized as an important cause of dilated cardiomyopathy (DCM). The diagnosis of HIV-related DCM carries a poor prognosis, with a mortality hazard ratio of 4.0 when compared with uninfected controls with idiopathic DCM.[65] Myocarditis and HIV-1 infection are the most studied causes of DCM in HIV disease.[66]

Before the advent of antiretroviral therapy, global left ventricular dysfunction was detected by echocardiography in 15% of HIV patients who were selected randomly in one study.[67] In almost all cases, myocardial biopsy revealed myocarditis with cardiotropic viral infection.[68] In autopsy studies of patients with HIV, myocarditis was identified in more than 50% of the 71 patients evaluated, and biventricular dilatation was present in 10% of cases.[69]

Zidovudine may cause mitochondrial myopathy in skeletal muscles, providing a possible link to involvement of myocardial muscle.[70] Studies performed on transgenic mice suggest that zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructures and with inhibition of cardiac mitochondrial DNA replication.[71] Clinical studies on AZT have been mixed, showing both association[72] and no association with LV dysfunction.[73,74]

Many organisms, such as herpes simplex virus,[75] cytomegalovirus, *Mycobacterium tuberculosis, Mycobacterium avium,*[76] *Cryptococcus neoformans,*[77] *Toxoplasma gondii,*[78] and *Histoplasma capsulatum,* may cause pericarditis and myocarditis in HIV-infected individuals. In one autopsy series, cardiac toxoplasmosis was diagnosed at autopsy in 21 of 182 (12%) of HIV-infected patients.[80] In another autopsy series performed before the introduction of potent combination ART, myocarditis was documented in 40% to 52% of patients who died of AIDS.[79] In more than 80% of these patients, no specific etiologic factor was found, whereas the remaining cases were attributable to the previously mentioned infectious agents.[79]

The introduction of potent ART regimens seems to influence the course of HIV-associated DCM, with a decreasing rate of mortality from heart failure. In a study performed in 1999 involving 105 ambulatory HIV patients, the prevalence of myocardial systolic dysfunction was low (3%) and none of the patients developed end-stage DCM.[80] The authors suggest a myocardial protective effect of antiretroviral therapy to explain this low prevalence of cardiac dysfunction compared with previous studies.[80] A decrease in the prevalence of global cardiac involvement has been shown in a retrospective study comparing HIV-positive patients treated with ART with those treated with NRTIs.[81]

The exact pathogenesis of DCM in the setting of HIV infection remains unknown and may involve direct effects of HIV on the heart, toxic effects from antiretroviral therapy, opportunistic infections, illicit drug use, nutritional disorders, and increased cytokine activity.[82]

Treatment of DCM in HIV patients has not been specifically studied; however, again by extrapolation of studies from HIV-negative patients, diuresis, afterload reduction with ACE-inhibitors, β-blocker therapy, and digoxin would appear

to be beneficial. Discontinuation of possible contributing substances, such as alcohol, cocaine, methamphetamine, and NRTI medication, as mentioned earlier, should be considered. IV immunoglobulin therapy may serve to improve left ventricular structure and function in HIV-infected patients.[83] Only a few cases have been reported in the literature regarding the use of left ventricular assist devices[84] or heart transplant in HIV-infected individuals.[85]

PERICARDIAL DISEASE IN PATIENTS WITH HIV INFECTION

Pericarditis in HIV-infected patients may present with large effusions and often with cardiac tamponade.[86-88] The incidence of pericardial effusion in patients with asymptomatic AIDS (defined as patients with CD4 < 200 cells/mm^3) was 11% per year before the introduction of effective ART.[88] The survival of AIDS subjects with effusion was significantly shorter (36% at 6 months) than the survival of AIDS subjects without effusions (93% at 6 months). In HIV patients, culture of pericardial fluid is often unrevealing. There are isolated case reports of pathogens, such as *Mycobacterium tuberculosis,*[89-91] staphylococcus,[92,93] *Cryptococcus neoformans,*[94] and herpes simplex,[95] as causes of pericarditis. The incidence of pericardial effusions after the introduction of HAART has not been evaluated, and treatment and evaluation of effusions in the HIV+ subject is similar to that in uninfected subjects involving echocardiography and pericardiocentesis, if indicated.

HIV-RELATED PULMONARY HYPERTENSION

The incidence of HIV-associated pulmonary hypertension before the advent of HAART was 1% to 2%.[96] The pathogenesis of HIV-associated pulmonary hypertension remains unclear. In patients without HIV infection, a report linked infection with human herpesvirus 8 (HHV-8) to primary pulmonary hypertension.[97] HHV-8 is one of the causal agents for Kaposi's sarcoma[98]; although only a small fraction of patients infected with HHV-8 develop Kaposi's sarcoma, the magnitude of immunosuppression predicts risk.[99] The seroprevalence of HHV-8 remains high in populations at risk for HIV.[100] For patients with HIV, HHV-8 may thus be a causative agent for pulmonary hypertension, but this has not yet been demonstrated.

The effect of antiretroviral infection on pulmonary hypertension is not known; however, in a recent report from the Swiss Cohort Study, pulmonary artery pressure increased in untreated patients but decreased in patients treated with HAART.[101] The oral endothelin receptor antagonist, bosentan, improved exercise tolerance and hemodynamic measurements in a small study of HIV patients.[102]

SUMMARY

With the number of HIV-infected adults increasing and HIV patients continuing to live longer, cardiovascular complications specific to HIV-infected individuals will represent an increasingly important health issue for physicians. Many of the long-term side effects of HIV infection and HIV medication remain unknown. Although studies on these issues are ongoing, physicians should remain aware of the possibility of HIV-associated cardiovascular complications in their patients with HIV infection, especially atherosclerosis, and treat all risk factors aggressively.

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Rehabilitation of the Patient with Cardiovascular Disease

Jonathan N. Myers and Victor F. Froelicher

CHAPTER CONTENTS

Before the 1970s, patients were completely immobilized after a myocardial infarction (MI) for 6 weeks or longer; the prevailing view was that this time period was necessary for complete healing of the myocardium. The post-MI patient was generally not expected to return to normal occupational or recreational activities. The process known as cardiac rehabilitation evolved in order to restore the patient to optimal physical, psychological, and social function. A significant body of data over the past 3 decades has documented both the benefits of early ambulation, as well as the numerous detrimental effects of strict bed rest. The act of merely sitting in the upright position has been shown to reduce the detrimental effects of remaining supine.[1] Both the indications for and scope of cardiac rehabilitation services have broadened. Advances in the treatment of cardiovascular diseases and data supporting the value of secondary prevention have greatly increased the spectrum of patients who may benefit from cardiac rehabilitation. This spectrum of patients now includes not only post-MI patients (both ST-elevation and non-ST-elevation) but also post–cardiac transplantation patients; post–percutaneous coronary intervention (PCI, stent implantation, angioplasty) patients; patients with chronic heart failure (CHF), implantable cardioversion devices (ICDs), and pacemakers. In addition, it is now widely recognized that exercise is only one component of cardiac rehabilitation.

The objectives for patients include not only preventing the effects of deconditioning but also improving functional capacity; relieving symptoms; and providing education, risk factor reduction, assistance in returning to normal activities, and psychosocial support. Societal objectives include decreasing health care costs by reduction in treatment time; reduction of medications; and prevention of premature disability, thus maintaining individual productivity and lessening the need for societal support. It is noteworthy in this context that randomized exercise trials, when combined, have shown that the rate of mortality from cardiovascular causes (defined as fatal reinfarction or sudden cardiac death) is reduced 20% to 25% among patients participating in rehabilitation. Even with major advances in the treatment of acute MI (e.g., thrombolytic therapy), updates of the meta-analyses of the trials performed from the 1970s through the 1990s have shown 25% to 30% reductions in mortality with rehabilitation.[2-4]

PHYSIOLOGIC EFFECTS OF IMMOBILITY

Data published since the late 1960s on the deleterious physiologic effects of bed rest have been an important stimulus for the growth of cardiac rehabilitation and contributed to an appreciation of its benefits. It is now widely recognized that the negative effects of bed rest include not only reductions in functional capacity but also adverse hemodynamic changes, alterations in cardiac size and function, orthostatic intolerance, and increased risk of thrombus formation. Patients hospitalized for cardiac events today are encouraged to begin physical activities as soon as possible. Simply exposing the patient to orthostatic stress and early ambulation counteracts the negative physiologic effects of prolonged bed rest and also provides the patient with tangible affirmation of improvement and increased self-confidence.

PHYSICAL TRAINING

Regular exercise increases work capacity; hundreds of studies have documented greater exercise capacity among active persons than among sedentary individuals. In general, patients with cardiovascular disease are equally able to benefit from exercise training. Although there are some notable differences, the mechanisms underlying the response to training are similar between those with and those without cardiovascular disease. The magnitude of the improvement in exercise capacity with training varies widely, generally ranging from 5% to 25%, but increases as large as 50% have been reported. The degree of change in peak oxygen uptake ($\dot{V}O_2$) depends primarily on the patient's initial state of fitness, but it is also affected by age and the type, frequency, and intensity of training. Peak $\dot{V}O_2$ may be as low as 10 to 15 mL/kg/min in patients with severe cardiovascular disease, and values as high as 80 to 90 ml/kg/min have been observed among elite endurance athletes.

The physiologic benefits of a training program can be classified as morphologic, hemodynamic, and metabolic (Table 49–1). Many animal studies have demonstrated significant morphologic changes with training including

Table 49–1 Physiologic Adaptations to Physical Training in Humans

Morphologic Adaptations
Myocardial hypertrophy (generally only in younger, healthy subjects)
Hemodynamic Adaptations
Increased blood volume
Increased end-diastolic volume
Increased stroke volume
Increased cardiac output
Decreased heart rate for any submaximal workload
Metabolic Adaptations
Increased mitochondrial volume and number
Greater muscle glycogen stores
Enhanced fat utilization
Enhanced lactate removal
Increased enzymes for aerobic metabolism
Increased maximal oxygen uptake

myocardial hypertrophy with improved myocardial function, increases in coronary artery size, and increases in the myocardial capillary-to-fiber ratio. However, such changes have been difficult to demonstrate in humans.[5,6] The major morphologic outcome of a training program in humans is probably an increase in cardiac size. However, although this adaptation has been demonstrated by many investigators among young, healthy individuals, it is unlikely to occur among older subjects (e.g., older than 40 years) or in patients with cardiovascular disease. Hemodynamic changes after training include reductions in heart rate at rest and any matched submaximal workload. For the patient with coronary artery disease, this is beneficial in that it results in a reduction in myocardial demand during activities of daily living. Other hemodynamic changes that have been demonstrated after training include reductions in blood pressure, increases in blood volume, and increases in maximal cardiac output; the latter underlies an increase in maximal oxygen uptake. In patients with heart disease, the major physiologic effects of training occur in the skeletal muscle. The metabolic capacity of the skeletal muscle is enhanced through increases in mitochondrial volume and number, capillary density, and oxidative enzyme content. These adaptations enhance perfusion and the efficiency of oxygen extraction.[6]

Newer Concepts Regarding Physiologic Benefits of Exercise Training

The effects of exercise training on the coronary vasculature have long been of interest. Although the hypothesis that training might reverse or retard the progression of atherosclerosis in humans had generally been abandoned, contemporary studies performed in patients with coronary artery disease (CAD) indicate that exercise training, when combined with multidisciplinary risk management, can improve myocardial perfusion.[7-9] This has been demonstrated indirectly using nuclear imaging[7] and directly by angiography.[8,9] Because most of these studies involved multifactorial risk reduction (e.g., diet, smoking cessation, stress management, pharmacologic management of risk factors) in addition to exercise, it is not possible to determine the independent effects of exercise training.

The mechanism by which the apparent improvement in myocardial perfusion might occur following training has stirred debate. Generally, it is considered unlikely that changes in coronary blood flow during exercise observed in animals would apply to humans. Three mechanisms could potentially explain an improvement in perfusion after training: (1) direct regression of atherosclerotic lesions; (2) formation of collateral vessels; or (3) a change in the dynamics of epicardial flow via flow-mediated or endogenous stimuli of the vessel. Evidence of small but significant improvements in lumen diameter after intensive exercise and risk-reduction programs in patients with CAD exist, but there is no evidence that collateral vessel formation occurs after training in humans. Interestingly, although changes in lumen diameter after these intervention programs are quite small, they are associated with considerable reductions in hospital admissions for cardiac reasons.[9] This suggests that patients in the intervention groups may achieve greater plaque stability without large changes in the coronary artery lumen.

A significant amount of research has demonstrated that training improves endothelial function, thus permitting enhanced peripheral and coronary blood flow in response to exercise. This represents a paradigm shift in the pathophysiology of CAD. We are now aware that the luminal diameter of epicardial vessels changes rapidly in response to mechanical (flow-related) and endogenous or pharmacologic stimuli. Hambrecht et al[10] studied the effects of exercise training in patients with reduced ventricular function and reported that leg blood flow during acetylcholine infusion was enhanced compared with controls. The improvement after training was attributed to an increase in endothelium-dependent vasodilation with an increase in basal nitric oxide formation. In a subsequent study, these investigators demonstrated an improvement in endothelium-dependent vasodilation in epicardial vessels, as well as resistance vessels in patients with CAD. After 4 weeks of exercise training, there was a 29% increase in coronary artery flow reserve in comparison with the non–exercise control group.[11]

These findings have been confirmed by other groups[12-14] and suggest that exercise training may have a profound effect on the vasodilatory properties of the vascular endothelium. Further exploration into the effects of exercise training on the dynamic behavior of the endothelium is an important target area for future research in patients both with and without existing cardiovascular disease.

CARDIAC REHABILITATION AFTER A MYOCARDIAL INFARCTION

Changes in health care economics have drastically altered the way in which cardiac rehabilitation is implemented. Hospital stays are shorter, progression through the program is quicker, and much of "cardiac rehabilitation" as it was traditionally known has changed. Reimbursement patterns differ considerably from one state to another and from one program to another. With shorter periods of time for physicians to interact with and monitor patients, as well as to cover educational materials adequately, there is a greater need for structured

outpatient programs in the home or community. Traditionally, typical phases that were included in rehabilitation were phase I, which includes the coronary care unit and inpatient care during the first few days after the event; phase II, which involves convalescence, an outpatient program, or a home program; and phase III, which was usually a longer-term community-based or home program. The precise course of each program naturally depends on the individual's needs and clinical status.

Disability Due to Myocardial Infarction

Cardiovascular diseases are the leading cause of activity limitation and disabled worker benefits in the United States. In fact, CAD alone is responsible for almost one of five disability allowances paid by the Social Security Administration. However, the total economic impact results from the combination of Social Security benefits, welfare support, disability insurance income, unemployment compensation, loss of taxable revenue, and reduced worker productivity related to cardiovascular diseases. From a purely economic standpoint, it is essential that patients with CAD be rehabilitated as quickly and efficiently as possible in order to enable their return to remunerative employment. Just as important, however, is amelioration of the psychosocial impact of heart disease including lessened depression and expedient return to pre-illness social roles in the family and community.

Historically, the patient's return to work, ability to drive, and sexual activity have been based on clinical judgments rather than on physiologic assessments. These decisions should be based on the consequence of the coronary event (e.g., ischemia, symptoms of CHF, dysrhythmias), the nature of the patient's occupational or recreational activities, and the response to the predischarge exercise test. In general, if the patient does not exhibit any untoward responses to submaximal exercise testing and achieves five or more metabolic equivalents (METs), it is unlikely that he or she will encounter difficulties during activities of daily living. More strenuous jobs or recreational requirements should not be initiated until a symptom-limited exercise test can be performed and exercise capacity can be determined and related to the desired physical activities of the patient.

Factors that influence a patient's return to work include age; work history; severity of cardiac damage; financial compensation for illness; employer's ignorance about the patient's abilities; termination of employment; and, most important, the patient's perception of his or her clinical status. Efforts of the rehabilitation team to develop a positive attitude and a sense of well-being for the patient may assist appropriate vocational adjustments. The physician's attitude also greatly affects the patient's return to work; encouragement can be beneficial.

In-Hospital Exercise after a Coronary Event

The purpose of beginning cardiac rehabilitation immediately is to counteract the negative effects of deconditioning rather than to promote training adaptations. It also provides an ideal time to begin education and psychological support. These first 3 to 5 days after an MI or bypass surgery are critical for beginning these processes. The literature is replete with studies documenting the efficacy and safety of beginning activities and education soon after a coronary event in stable patients.[15] Appropriate activities initially include sitting at the bedside, active range of motion exercises, self-care, and progressing to ambulation around the hospital unit under supervision and later to climbing a flight of stairs.

Patient Education

Education should be initiated before physical activities are begun; the patient may lack self-confidence and need affirmation that the activities are safe. Patient education during the acute phase usually consists of explanation about the coronary care unit, the cardiac rehabilitation program, symptoms, and the delivery of routine diagnostic and therapeutic modalities. The patient should be educated as to the limitations imposed by the disease, potential for improvement, and precautions to be observed. The program must be individualized for the patient depending on his or her psychosocial status. Clinical status is determined largely by the severity of the MI, but the medical history must also be considered.

Exercise Testing before Hospital Discharge

Performing an exercise test before hospital discharge provides much useful information including clarification of the response to exercise, development of an exercise prescription, and recognition of the need for medications or interventions. It can also have a beneficial psychological impact on recovery and begins the rehabilitation process. The test is considered the first step in the outpatient cardiac rehabilitation exercise program.

Experts have debated whether the predischarge test should be performed to a maximal level and whether it should be performed in patients with ST-elevation MIs. Available data indicate that it is safe to perform maximal or near-maximal testing in most post-MI patients, although a distinction has not been made for the presence or absence of ST-elevation MIs. The predischarge test has generally been submaximal, but the appropriate "submaximal" endpoint has varied. Traditionally, the test is stopped at a level not exceeding 5 METs or a Borg perceived exertion level of 16. In many hospitals a submaximal target heart rate is used (e.g., 110 beats/min for patients taking β-blockers). The protocol should be modified to accommodate the reduced exercise tolerance of most patients recovering from a myocardial infarction; individualized ramp or Naughton protocols are preferable.[16] Later, when return to full activities is intended, the test can be symptom and sign limited.

The prognostic value of the predischarge test has been widely studied. A meta-analysis has shown that an abnormal exercise capacity or abnormal systolic blood pressure responses are better predictors of increased risk than is ST-segment depression.[17] However, ST-segment depression probably indicates increased risk in men who do not take digoxin and whose resting ECG does not show extensive damage. The criterion of 2 mm or more of ST-segment depression, along with symptoms or abnormal hemodynamic responses, appear to be useful for identifying higher-risk patients who should be considered for cardiac catheterization and possibly revascularization.

Outpatient Cardiac Rehabilitation

Multiple approaches to outpatient rehabilitation have been employed. Traditionally, this phase begins 1 to 2 weeks after discharge from the hospital and may last from 1 to 4 months. Most commonly, patients attend group exercise sessions three times per week; however, frequency of exercise is often modified by the individual patient's overall goals, functional capabilities, reimbursement, proximity to the hospital or clinic, and personal commitment. The first few exercise sessions usually emphasize warm-up and cool-down activities with only a modest aerobic component. A symptom-limited maximal exercise test is often recommended approximately 6 weeks after hospital discharge to determine appropriate activity limitations.

Changes in reimbursement patterns have changed outpatient programs more than other components of cardiac rehabilitation. In many instances only a few exercise or educational sessions are reimbursed. The transition from an outpatient to a home-based maintenance program now occurs more rapidly. Randomized trials have demonstrated that patients can return to work quickly and safely during rehabilitation and that participation in rehabilitation assists this process. DeBusk and colleagues[18] pioneered the application of home rehabilitation programs in the 1980s; these programs use either unmonitored or monitored surveillance via telephone or microprocessor. Home programs are now widely used, and their safety and efficacy have been shown to be similar to those of more conventional programs.

Safety of Cardiac Rehabilitation

The safety of outpatient cardiac rehabilitation has been well documented. Van Camp[19] gathered data from 167 randomly selected cardiac rehabilitation centers on more than 51,000 patients who exercised more than 2 million hours. Over a 4-year period there were only 21 cardiac resuscitations (3 of which failed) and 8 myocardial infarctions. This amounts to 8.9 cardiac arrests, 3.4 infarctions, and 1.3 fatalities per million hours of patient exercise. Surprisingly, ECG monitoring had little influence on complications, which suggests that the additional expense of telemetry may not be necessary. In a 16-year follow-up from William Beaumont Hospital in Michigan, 292,254 patient exercise hours were recorded in phase II and III programs.[20] During this period, only 5 major cardiovascular complications occurred, representing a rate of 1 per 58,451 patient exercise hours. Despite the low incidence of these events, appropriate medical personnel trained in the use of automated external defibrillators must be available to respond when events do occur.

Monitoring in Outpatient Rehabilitation

Experts now recognize that only a small percentage of patients require continuous ECG monitoring during exercise. Efforts to reduce the cost of rehabilitation, in addition to the recognition that most patients can exercise quite safely without continuous telemetry, have brought about this change. Table 49–2 lists the criteria for ECG monitoring outlined in the American College of Cardiology Position Statement on Cardiac Rehabilitation.[21]

Table 49–2 American College of Cardiology Criteria for Electrocardiographic Monitoring during Cardiac Rehabilitation

1. Severely depressed left ventricular function (ejection fraction < 30%)
2. Resting complex ventricular arrhythmia (Lown type 4 or 5)
3. Ventricular arrhythmias appearing or increasing with exercise
4. Decrease in systolic blood pressure with exercise
5. Survivors of sudden cardiac death
6. Patients following myocardial infarction complicated by congestive heart failure, cardiogenic shock, and/or serious ventricular arrhythmias
7. Patients with severe coronary artery disease and marked exercise-induced ischemia
8. Inability to self-monitor intensity due to physical or intellectual impairment

From American College of Cardiology: Position paper on cardiac rehabilitation. J Am Coll Cardiol 1986;7:451-3.

Maintenance Program

Progression to an out-of-hospital maintenance program is desirable to maintain training adaptations and to help prevent recurrence of events or symptoms. The period of time required before patients move from a supervised program to a maintenance program can vary considerably, depending on reimbursement, patient stability, exercise capacity, and individual patient needs, but it rarely exceeds 12 weeks. The patient must understand how to monitor his or her own exercise intensity, understand how to recognize symptoms, and have a basic knowledge of his or her particular disease and medications. When making occupational activity recommendations for patients, it can be helpful to know the estimated energy requirements of various activities (Table 49–3). This way, appropriate recommendations can balance the patient's functional limitations with the need to return work, desire to continue recreational activities, or both.

Performing an exercise test before the maintenance program is essential in order to provide an outgoing exercise prescription, confirm the safety of exercise for a given patient, and assess risk for future cardiac events. Funding for this phase must often be borne by the patient because most types of health insurance do not cover it.

Exercise Prescription for Outpatient Rehabilitation

The American College of Sports Medicine defines exercise prescription as " … the process whereby a person's recommended regimen of physical activity is designed in a systematic and individualized manner."[22] An "individualized manner" implies the establishment of specific strategies to optimize return to work or activities of daily living, reduction of risk factors for future cardiac events, and maximization of the patient's capacity to maintain an active lifestyle. The development of an appropriate exercise prescription to meet

Table 49–3 Energy Costs of Various Occupational and Recreational Activities

	Occupational	Recreational
1 to 2 METs	Desk work, auto driving, typing	Standing, walking (1 mph), playing cards, sewing, knitting
2 to 3 METs	Auto repair, radio, janitorial work, bartending	Level walking (2 mph), level bicycling (5 mph), riding lawnmower, billiards, bowling, shuffleboard, woodworking (light), powerboat driving, golf (power cart), canoeing (2.5 mph), horseback riding (at a walk), playing piano and other musical instruments
3 to 4 METs	Bricklaying, plastering, using a wheelbarrow (light load), machine assembly, welding (moderate load), cleaning windows	Walking (3-3.5 mph), cycling (8 mph), table tennis, golf (carrying clubs), dancing, badminton (singles), tennis (doubles), raking leaves, hoeing, many calisthenics
4 to 5 METs	Digging gardens, shoveling light earth	Walking briskly (4 mph), cycling (10 mph), canoeing (4 mph), horseback riding, stream fishing, ice or roller skating (9 mph)
6 to 7 METs	Shoveling (10 lb), carrying objects 50-75 lb, using heavy power tools	Walking quickly (5 mph), cycling (11 mph), playing badminton (competitive) and tennis (singles), splitting wood, shoveling snow, hand lawn mowing, folk dancing, light downhill skiing, ski touring (2.5 mph), water skiing
7 to 8 METs	Digging ditches, carrying 80 lb, sawing hardwood	Jogging (5 mph), cycling (12 mph), horseback riding (at a gallop), vigorous downhill skiing, basketball, mountain climbing, ice hockey canoeing (5 mph), touch football, paddleball
8 to 9 METs	Moving or pushing heavy objects > 75 lb	Running (5.5 mph), cycling (13 mph), ski touring shoveling (14 lb), baling hay (4 mph, loose snow), squash (social), handball (social), fencing, basketball (vigorous)
10^{+} METs	Shoveling > (16 lb), firefighting—climbing ladder in full gear	Running: 6 mph = 10 METs; 7 mph = 11.5 METs; 8 mph =13.5 METs; 9 mph = 15 METs; 10 mph = 16 METs; ski touring (5+ mph), handball (competitive), racquetball (competitive)

MET, maximal exercise test.
From Ainsworth BE, Haskell WL, Leon AS, et al: Compendium of physical activities: Classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71-80.

the individual patient's needs has a sound scientific foundation,[15,22,23] but there is also an art to effective exercise programming. No single program is best for all patients or even one patient over time; capabilities, vocational needs, and expectations differ among patients and can change with the passing of time. Thus, the art of exercise prescription relies on the physician's or exercise physiologist's abilities to synthesize pathophysiologic, psychosocial, and vocational factors and tailor the exercise prescription to the patient's needs and realistic goals. A final but important consideration is the selection of activities that the individual enjoys and will be more likely to continue to perform after the formal rehabilitation program ends.

Principles of Exercise Prescription

Training implies chronic adaptations of the body to the demands placed on it. A training effect is best measured as an increase in peak $\dot{V}O_2$, but not all institutions have gas exchange equipment, and there are many ways of quantifying functional outcomes of rehabilitation. For example, after rehabilitation some patients may be better suited to carry out submaximal levels of activity for longer periods, remain independent, continue working, or rejoin their friends on the golf course. All of these can be important goals for a given patient and may occur even with a minimal change in peak $\dot{V}O_2$.

The major components of the exercise prescription are the frequency, intensity, duration, mode, and the rate of progression. In general, these principles apply for both the patient with heart disease and the healthy adult; however, the ways in which they are applied differ. It is generally accepted that increases in $\dot{V}O_2$ max are achieved if a person exercises dynamically for a period ranging from 15 to 60 minutes, 3 to 5 times per week, at an intensity equivalent to 50% to 80% of their maximum capacity. Dynamic exercises are those that employ large muscle groups in a rhythmic manner, such as treadmill walking, cycle ergometry, rowing, stepping, and arm ergometry. Short warm-up and cool-down periods are strongly encouraged for participants in cardiac rehabilitation programs.

Much of the art of exercise prescription involves individualizing exercise intensity. Typically, exercise intensity is expressed as a percentage of maximal capacity, either in absolute terms (i.e., workload or watts) or in relation to the maximal heart rate, maximal oxygen uptake, or perceived effort. Training benefits have been shown to occur with the use of exercise intensities ranging from 40% to 85% of maximal oxygen uptake, which are generally equivalent to 50% to 90% of maximal heart rate. However, the intensity that a given individual can maintain for a specified period of time varies widely. In general, the most appropriate intensity for most patients in rehabilitation programs is 50% to 70% of

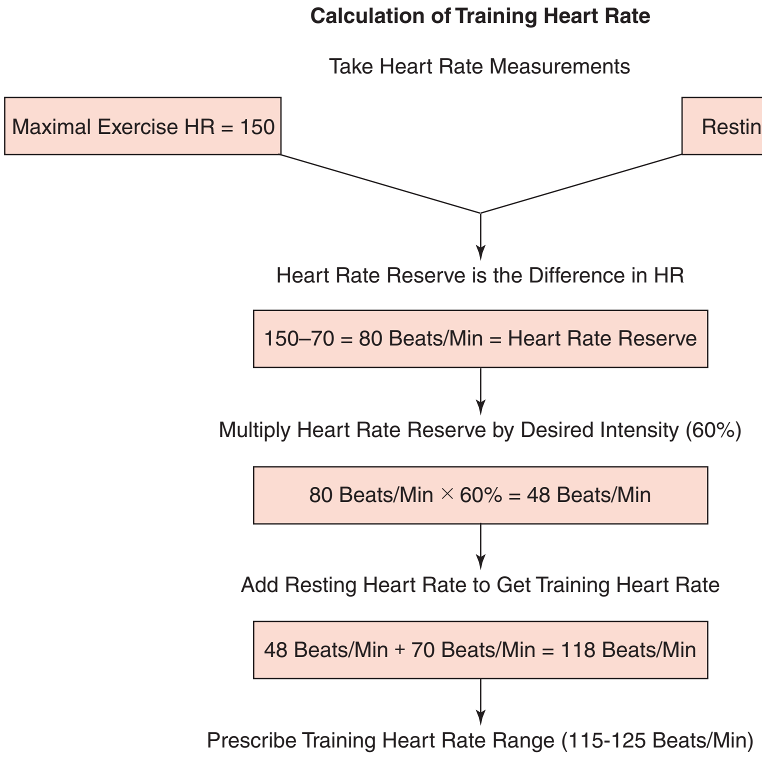

Figure 49–1 Flow diagram for development of an exercise prescription using heart rate in a typical patient initiating a rehabilitation program.

maximal capacity. The actual prescribed exercise intensity for the patient should naturally depend on goals, health status, length of time since infarction or surgery, symptoms, and initial state of fitness.

Training is a general phenomenon; there is no true threshold beyond which patients achieve benefits. Thus, as long as patients exercise safely, setting the exercise intensity is a less rigid practice than it was years ago. In addition, the patient's ability to tolerate activities can change daily. Other factors, such as time of day, environment, and time since medications were taken, can influence the patient's response to exercise, and the exercise prescription must be adjusted accordingly. It is also useful to employ a window of intensity that ranges approximately 10% above and 10% below the desired level.

The graded exercise test is the foundation on which a safe and effective exercise prescription is based. To achieve a desired training intensity, oxygen uptake or some estimation of it must be quantified during a maximal or symptom-limited exercise test. Because heart rate is easily measured and is linearly related to oxygen uptake, it has become a standard by which training intensity is estimated during exercise sessions. The most useful method is known as the *heart rate reserve*. This method uses a percentage of the difference between maximal heart rate and resting heart rate and adds this value to the resting heart rate. An example of a typical patient given an exercise prescription at 60% of the heart rate reserve is illustrated in Figure 49–1. This is also referred to as the *Karvonen formula* and is reliable in patients with normal sinus rhythm whose measurements of resting and maximal heart rates are accurate. An estimated target heart rate for exercise should be supplemented by considering the patient's MET level relative to his or her maximum, the perceived exertion, and symptoms.

Contraindications to Exercise Training

Absolute contraindications include unstable angina pectoris, aortic dissection, complete heart block, uncontrolled hypertension, decompensated heart failure, uncontrolled dysrhythmias, thrombophlebitis, and other complicating illnesses that prevent exercise. Relative contraindications include frequent premature ventricular contractions, controlled dysrhythmias, intermittent claudication, metabolic disorders, and moderate anemia or pulmonary disease. Studies show that if these contraindications are considered, the incidence of exertion-related complications in cardiac rehabilitation programs is extremely low and, because of the availability of rapid defibrillation, serious events rarely occur.

Rehabilitation in Patients with Chronic Heart Failure

Until the late 1980s, stable CHF was considered by many authorities to be a contraindication to participation in an exercise program. Today it is known that patients with CHF derive considerable benefits from cardiac rehabilitation. Randomized trials performed during the 1990s indicate that the major physiologic benefit from training in CHF occurs in the skeletal muscle rather than in the heart itself.[24]

The clinical approach to the patient with CHF who is considered for a rehabilitation program is similar to that for the post-MI patient described earlier, although several important differences are worth noting. Patients must be stable, and those exhibiting significant dyspnea with exertion, peripheral edema, or other signs indicative of right-sided failure should be deferred until the absence of these signs is assured. The potential for complications during exercise may be higher in patients with CHF relative to patients with normal left

ventricular function. A greater number of medications that can influence exercise responses including vasoactive, antiarrhythmic, inotropic, and β-blocking agents should be considered. Exercise capacity tends to be significantly lower than that in the typical patient with coronary disease. Numerous hemodynamic abnormalities underlie the reduced-exercise capacity in CHF including impaired heart rate responses, inability to distribute cardiac output normally, abnormal arterial vasodilatory capacity, abnormal cellular metabolism in skeletal muscle, elevated systemic and pulmonary vascular resistance, and ventilatory abnormalities that increase the work of breathing and cause exertional dyspnea.[24,25] Studies suggest that many of these abnormalities can be improved by exercise training.[24]

Most patients with reduced left ventricular function who are clinically stable (including the absence of signs of right-sided failure, absence of significant dyspnea on exertion, and absence of peripheral edema) and have reduced exercise tolerance are candidates for exercise programs. Excluding patients with signs and symptoms of right-sided failure or treating them judiciously before entry into a program is often necessary. An exercise test is particularly important before initiating the program to ensure safety of participation. Rhythm abnormalities, exertional hypotension, or other signs of instability should be ruled out. Expired gas exchange measurements are particularly informative in this group because they provide an improvement in accuracy and permit an assessment of ventilatory abnormalities that are common in this condition.[24,25] ECG monitoring during exercise is more often indicated in this group. Attention should be paid to daily changes in body weight, rhythm status, and symptoms.

Increasing numbers of patients have undergone cardiac transplantation for end-stage heart failure, and today approximately three quarters of these patients remain alive after 5 years. Several reports have addressed the effects of training after cardiac transplantation. These studies have demonstrated increases in peak oxygen uptake, reductions in resting and submaximal heart rates, and improved ventilatory responses to exercise.[26,27] The combination of improved cardiac function, changes in skeletal muscle metabolism, and improvements in strength contributes to improved exercise tolerance with training in these patients.

Meta-Analyses of Survival after Cardiac Rehabilitation

The overall benefits of cardiac rehabilitation are now widely accepted. Comprehensive reviews confirming these benefits are available.[5,15,24] Because none of the single-center studies alone have been sufficiently powered to adequately document changes in mortality, a series of meta-analyses has been performed to evaluate the impact of cardiac rehabilitation on fatal and nonfatal events. O'Connor and colleagues[28] performed a meta-analysis of 22 randomized trials of cardiac rehabilitation involving 4554 patients. They found a 20% reduction of risk for total mortality, a 22% reduction for cardiovascular mortality, and a 25% reduction in the risk for fatal reinfarction. Oldridge and associates[29] performed a similar meta-analysis with 10 randomized trials that included 4347 patients and found a similar reduction for all-cause and cardiovascular mortality in the patients undergoing cardiac rehabilitation. The pooled odds ratios for the combined studies suggest 24% and 25% reductions in all-cause and cardiovascular deaths, respectively, among the exercise groups. Criticisms of these analyses are that each of the pooled studies was not uniform in its treatment of patients and that a nonexercise intervention done in the different trials may have biased the results. Nevertheless, these two meta-analyses have been widely cited and have been highly influential in support of cardiac rehabilitation.

Taylor and colleagues[2] performed an updated meta-analysis of rehabilitation trials among patients with coronary heart disease. The aforementioned studies focused on studies performed during the 1970s and 1980s, but the latter study included trials up to 2003. A total of 48 trials involving 8940 patients met the inclusion criteria. Compared with usual care, cardiac rehabilitation was associated with reduced all-cause mortality (odds ratio [OR] = 0.80) and cardiac mortality (OR=0.74). In addition, participation in cardiac rehabilitation was associated with greater reductions in cholesterol, triglycerides, and systolic blood pressure. However, there were no differences between rehabilitation and usual care groups in nonfatal reinfarctions or revascularization rates. Importantly, the effect of rehabilitation on mortality was independent of CHF diagnosis, type of rehabilitation, dose of exercise intervention, length of follow-up, trial quality, or trial publication date.

Although the mortality effects of exercise-based rehabilitation on outcomes in post-MI patients have been known for some time (i.e., since the 1980s), meta-analyses among patients with CHF have only recently been performed. Until the late 1980s, activity was generally restricted in patients with CHF, due largely to concerns over safety and unknown effects on the myocardial remodeling process. During the 1990s numerous trials demonstrated that exercise training is safe for these patients, and several landmark trials were published that used highly technologic imaging techniques which allayed concerns over the effects of training on left ventricular remodeling.

A collaborative study (the ExTraMATCH study) of European centers that performed exercise training trials in patients with CHF during the 1990s has been completed.[3] This meta-analysis included controlled exercise trials in CHF and was designed to provide estimates of treatment benefits on mortality and hospital admission. Nine trials met the study inclusion criteria, comprising a total of 395 exercise intervention patients and 406 controls. After a mean follow-up period of 705 days, it was found that exercise training reduced mortality by 35% and reduced the composite outcome of death or hospital admission by 28%. Moreover, there was no evidence that any subgroup (elderly, severely reduced exercise capacity or ventricular function, type of CHF, duration of training, or gender) was less likely to benefit from training.

EVOLVING LANDSCAPE FOR CARDIAC REHABILITATION

Early and progressive ambulation of patients after a myocardial infarction is now considered routine care. Despite many new therapies in cardiovascular medicine, cardiac rehabilitation maintains an important place in reducing morbidity and mortality.[2,3,4,15,28,29] The controlled trials, when combined, demonstrate that the efficacy of rehabilitation in reducing

mortality is similar to the best medical interventions.[15] Moreover, cardiac rehabilitation has redirected interest to humanistic concerns, providing a balance to the emphasis on complex technology. It also provides an ideal environment for patient supervision and for ensuring stability after an interventional procedure. Guidelines now regard cardiac rehabilitation as an appropriate medium for comprehensive risk reduction and secondary prevention.[30] Available data suggest that cardiac rehabilitation is economically sound.[31,32]

Medicine is presently experiencing an evolution toward technologic efficacy and outcomes assessment. Health economists and legislators are reexamining the value placed on all forms of medical care. Although this movement has changed the way that cardiac rehabilitation is implemented, studies have confirmed its value. Some of the ways in which the current economic environment has changed cardiac rehabilitation include a lessening of direct ECG monitoring, shorter hospital stays, and a more rapid progression to home programs. The frequency of interventions has lessened the morbidity associated with myocardial infarction. Data on efficacy, safety, and technologic advances in the treatment of cardiovascular disease have shown that cardiac rehabilitation has changed in such a way that a wider range of patients can benefit from these services than in the past. For example, patients with stable CHF, once excluded from cardiac rehabilitation programs, are now thought to be among those who benefit the most. Pacemaker, post-transplantation, post-bypass, post-valvular surgery, and claudicant patients now make up a significant fraction of the patients in many programs. Despite this fact, most eligible patients (up to 90%) fail to receive these services. Not all patients need all the components of cardiac rehabilitation, but directing these services to patients who need them the most remains one of the important challenges for the field.[33]

Lastly, there has been a change in the public health care message toward physical "activity" as inherently beneficial regardless of objective measurements of "fitness." This has caused a shift in focus from morbidity, mortality, and exercise capacity to issues related to maintaining an active lifestyle and optimizing the patient's capacity to perform the physical challenges offered by occupational or recreational activities.

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Appendix 1

Cardiovascular Drugs: Comprehensive Drug Tables

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GUIDE TO INTERPRETATION OF COMPREHENSIVE DRUG TABLES

The comprehensive drug tables that follow are arranged generally in the sequence of the chapters in this textbook. They are meant to serve as a reference and guide to clinicians. However, it remains the responsibility of every clinician to evaluate the appropriateness of therapy and dosing in the context of the clinical situation of an individual patient. When dealing with new therapeutic agents, clinicians should familiarize themselves with the appropriate indications, dosing, and monitoring recommendations such as those found in the corresponding chapters in this textbook, as well as in the literature citations that are provided.

Table A1–1

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
I. β-Blockers										
Acebutolol	40%	1.2 ± 0.3 L/kg	30-36%	Hepatic/renal	3-4 hr	200-1200 mg/day in 1-2 divided doses	NS		Drug has ISA	
Atenolol	50%	0.95 ± 0.15 L/kg	6-16%	Renal	6-9 hr	PO: 25-100 mg PO q.d. IV: MI (myocardial infarction) 5 mg IV over 5 min followed by another 5 mg injection 10 min later	NS		Avoid use in patients with CrCl <30 mL/min	
Bisoprolol	80%	3.2 ± 0.5 L/kg	30%	Hepatic/renal	9-12 hr	HTN: 2.5-20 mg PO q.d. CHF: 1.25 mg PO q.d. to start, increase dose q 2 wk as tolerated to target dose of 10 mg or max tolerated dose	NS	Bradycardia, conduction abnormalities, hypotension, bronchospasm, blunting of hypoglycemia response (nonselective β-blockers may delay recovery from hypo-glycemia), weight gain, decreases maximum exercise tolerance, vivid dreams, decreased libido. Avoid initiating therapy among patients with decompensated CHF.		CIBIS-II Investigators and Committees: The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II). Lancet 1999;353:9-13.
Carvedilol	25-35%	1.5 ± 0.3 L/kg	95%	Hepatic (CYP 2D6 and 2C9)	7-10 hr	CHF: 3.125 mg PO b.i.d. to start, double dose q 2 wk as tolerated to target dose of 25 mg PO b.i.d. or max tolerated dose. Target dose 50 mg PO bid for patients >85 kg. HTN: 6.25 mg PO b.i.d. to start, up to 25 mg PO b.i.d. Post-MI LVD: 6.25 mg PO b.i.d. to start gradually titrated to target dose of 25 mg PO b.i.d.	Hypotensive (vasodilatory) effects may be increased by drugs that inhibit CYP 2D6: amiodarone, cimetidine, fluoxetine, haloperidol, paroxetine, propofenone, quinidine, and ritonavir. May increase serum digoxin and cyclosporine concentrations.		Take with food to minimize dizziness.	
Esmolol	N/A	1.9 ± 1.3 L/kg	55%	RBCs	9 min	Loading dose of 200-500 mcg/kg IV over 1 min, then 50-100 mcg/kg/min; titrate by 50 mcg/kg/min q 15-20 min. up to 200 mcg/kg/min	NS			

Labetalol	40%	9.4 ± 3.4 L/kg	50%	Hepatic	3-5 hr	PO: 100 mg PO b.i.d. to start; max dose of 2400 mg/day in 2-3 divided doses IV: 20 mg IV over 2 min, may give 20-80 mg at 5- to 10-min intervals up to 300 mg; CI of 0.5-2 mg/min	Cimetidine may increase oral bioavailability.	Bradycardia conduction abnormalities, hypotension, bronchospasm, blunting of hypoglycemia response (nonselective β-blockers may delay recovery from hypo-glycemia), weight gain, decreases maximum exercise tolerance, vivid dreams, decreased libido. Avoid initiating therapy among patients with decompensated CHF.		
Metoprolol	50%	4.2 ± 0.7 L/kg	12%	Hepatic (CYP 2D6)	3-4 hr	IV: (MI) 5 mg IV q 5 min × 3 doses PO: 50-400 mg/day in 2 divided doses (immediate release) or 1 dose (sustained release) CHF: metoprolol CR/XL 12.5-25 mg PO q.d., double dose q 2 wk as tolerated to target dose of 200 mg PO q.d. or max tolerated dose	Effect may be increased by the following drugs: amiodarone, cimetidine, fluoxetine, haloperidol, paroxetine, quinidine, and ritonavir.			MERIT-HF Study Group: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353: 2001-2007.
Nadolol	30%	1.9 ± 0.2 L/kg	30%	Renal	14-24 hr	20-320 mg PO q.d.	NS		Avoid using in patients with CrCl <30 mL/min	
Penbutolol	≈100%	ND	80-98%	Hepatic	5 hr	10-80 mg PO q.d.	NS		Drug has ISA.	
Pindolol	90%	2.3 ± 0.9 L/kg	40%	Hepatic	3-4 hr	10-60 mg/day in 2-3 divided doses	NS		Drug has ISA.	
Propranolol	35-70%	4.3 ± 0.6 L/kg	90%	Hepatic (CYP 2D6)	4 hr	PO: (immediate release) 20-320 mg/day in 2-4 divided doses PO: (sustained release) 60-320 mg/day in 1-2 divided doses. IV: 0.1 mg/kg divided into 3 doses given by slow IV push q 5 min	Effect may be increased by the following drugs: amiodarone, cimetidine, fluoxetine, haloperidol, paroxetine, quinidine, and ritonavir.			

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
Timolol	60%	2.1 ± 0.8 L/kg	10%	Hepatic (CYP 2D6)	4 hr	10 mg PO b.i.d to start, max dose is 60 mg/day in 2 divided doses	Effect may be increased by the following drugs: amiodarone, cimetidine, fluoxetine, haloperidol, paroxetine, quinidine, and ritonavir.			

Reference for β-blockers section: Lopez-Sendon J, Swedberg K, McMurray J, et al: Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on β-adrenergic receptor blockers. Eur Heart J 2004;25:1341-62.

ACE, angiotensin-converting enzymes; ACS, acute coronary syndrome; ACT, activated clotting time; aPTT, activated partial thromboplastin time; BP; blood pressure; CABG, coronary artery bypass graft; CBC, complete blood cell count; CHF, congestive heart failure; CI, continuous infusion; CrCl, creatinine clearance; CYP, cytochrome; DVT, deep vein thrombosis; ECG; electrocardiographic; Elim, elimination; ER; extended release; ESRD, end-stage renal disease; F, bioavailability; GI, gastrointestinal; HIT-2, heparin induced thrombocytopenia; HMG-CoA, hydroxy-3-methylglutaryl coenzyme A; HTN, hypertension; IC, intracoronary; INR, International Normalized Ratio; IR, immediate release; ISA, intrinsic sympathomimetic activity; IV, intravenous; LBW, lean body weight; LFT, liver function tests; LMWH, low-molecular-weight heparin; LV, left ventricular; LVD, left ventricular dysfunction; MAO, monoamine oxidase; max, maximum; MI, myocardial infarction; N/A, not applicable; NAPA, *N*-acetylprocainamide; ND, no data; NS, not significant; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; PE, pulmonary embolism; PKIN, pharmacokinetic; PTCA, percutaneous transluminal coronary angioplasty; RBC, red blood cell; RI, renal insufficiency; r-PA, reteplase; SC, subcutaneous; SCr, serum creatinine; SL, sublingual; SR, sustained release; $T_{1/2}$, half-life; t-PA, tissue-type plasminogen activator; UA/NSTEMI, unstable angina/non-ST segment elevation myocardial infarction; V_d, volume of distribution; VF, ventricular fibrillation; VT, ventricular tachycardia.

For further discussion, see Chapter(s) 5-12, 14, 31.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
II. Nitrates										
Isosorbide dinitrate	22%; may increase with long-term use, 75% for extended release	3.9 L/kg	28%	Hepatic	1 hr (ISDN), 4.6 hr (I5MN)	PO: 10-40 mg PO t.i.d Extended release: 40-160 mg/day			A nitrate-free interval of 12 hr is desirable to minimize nitrate tolerance. Absorption is increased when taken on an empty stomach.	
Isosorbide mononitrate	93%	0.7 L/kg	Minimal	Hepatic	5 hr	Immediate release tablet: 10-20 mg PO b.i.d. (doses 7 hr apart) Extended release: 30-240 mg PO q.d.	Avoid concomitant adminstration of sildenafil, tadalafil, or vardenafil	Headache, dizziness, reflex tachycardia, orthostatic hypotension, contact dermatitis with patch		Kirsten R, Nelson K, Kirsten D, et al: Clinical pharmacokinetics of vasodilators: part 2. Clin Pharmacokinet 1998:35:9-36.
Nitroglycerin	SL = 38 ± 26% Top = 72 ± 20%	3.3 L/kg	60%	Hepatic	1-4 min	SL: 0.3-0.4 mg, up to 3 doses in 15 min Topical: 0.5-2 inches q 6-8 hr Patch: 0.2-0.8 mg/h (maintain a nitrate-free interval of 12 hr to minimize tolerance) IV: 5-10 mcg/min to start; increase by 10 mcg/min q 3-5 min until relief of angina, fall in BP or PCWP. Max dose usually 200 mcg/min, although higher doses have been used IC: 50-200 mcg for coronary vasodilation				

For abbreviations, see p. 864. For further discussion, see Chapter(s) 5-12, 14.
ISDN, isosorbide dinitrate; I5MN, isosorbide-5-mononitrate.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
IIa. Additional Anti-anginal Agents										
Ranolazine	55%	ND	62%	Hepatic (CYP3A and 2D6)	7 h	500 mg PO b.i.d., may be titrated to max dose of 1000 mg PO b.i.d.	Effect of ranolazine may be increased by drugs that are potent and moderately potent inhibitors of CYP 3A which include (but is not limited to) the following: amiodarone, azole antifungals, clarithromycin, cyclosporine, diltiazem, erythromycin, grapefruit juice, imatinib, HIV protease inhibitors, verapamil. Medications that inhibit P-glycoprotein may increase the absorption of ranolazine. Ranolazine may increase digoxin concentrations.	↑ QT interval constipation, nausea, dizziness, headache	Ranolazine is contraindicated in patients taking other medications associated with prolongation of the QT interval. Ranolazine is contraindicated in patients with hepatic impairment and should not be used in patients with severe renal impairment.	Chaitman BR: Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. Circulation 2006; 113:2462-72.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
III. Dihydropyridine Calcium Channel Blockers										
Amlodipine	60-65%	21 L/kg	93%	Hepatic (CYP 3A4)	30-50 hr	2.5-10 mg PO q.d.	Concentrations of dihydropyridine calcium channel blockers may be increased by the following: amiodarone, azole antifungals, clarithromycin, delavirdine, erythromycin, fluoxetine, fluvoxamine, grapefruit juice, metronidazole, nefazodone, protease inhibitors, zafirlukast. Concentrations may be decreased by the following: barbiturates, carbamazepine, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin.	Hypotension, dizziness, flushing, headache, peripheral edema		Abernethy DR, Schwartz JB: Calcium-antagonist drugs. N Engl J Med 1999;341:1447-57.
Felodipine	20%	10 L/kg	>99%	Hepatic (CYP 3A4)	11-16 hr	2.5-20 mg PO q.d.				
Isradipine	15-24%	3 L/kg	95%	Hepatic (CYP 3A4)	8-12 hr	2.5-5 mg PO b.i.d.				
Nicardipine	35%	0.64 L/kg	95%	Hepatic (CYP 3A4)	2-4 hr	PO: (immediate release) 20-40 mg PO t.i.d. PO: (sustained release) 30-60 mg PO b.i.d. IV: (for patient previously receiving oral nicardipine) 20 mg PO q 8 hr = 0.5 mg/hr 30 mg PO q 8 hr = 1.2 mg/hr 40 mg PO q 8 hr = 2.2 mg/hr IV: (hypertansive emergency) 5-15 mg/hr				
Nifedipine	52 ± 37%	0.8 ± 0.1 L/kg	96%	Hepatic (CYP 3A4)	2-5 hr	Extended release: 30-90 mg PO q.d.				
Nimodipine	13%	1.7 L/kg	>95%	Hepatic (CYP 3A4)	1-2 hr	After subarachnoid hemorrhage: 60 mg PO q 4 hr × 21 days			Administer on an empty stomach to increase bioavailability.	
Nisoldipine	5%	4-5 L/kg	>99%	Hepatic (CYP 3A4)	7-12 hr	10-60 mg PO q.d.				

For abbreviations, see p. 864. For further discussion, see Chapter(s) 5-12, 30-40.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
IV. Nondihydropyridine Calcium Channel Blockers										
Diltiazem	40-60%	5.3 L/kg	77-93%	Hepatic	5 hr	PO: (immediate release) initially, 30-60 mg PO q 6-8 hr (max of 480 mg/day), once stable can convert to an equivalent dose of extended release PO: (extended release) 120-480 mg PO q.d. IV: (bolus dose) 0.25 mg/kg IV over 2 min, may repeat in 15 min with 0.35 mg/kg IV over 2 min IV: (infusion) 5-15 mg/h IC: 100-200 mcg for "no reflow" or "slow flow"	Inhibitor of CYP 3A4; leads to increases in concentrations of many drugs, including alprazolam, carbamazepine, cyclosporine, dihydropyridine calcium channel blockers, HMG-CoA inhibitors (atorvastatin, lovastatin, simvastatin), quinidine, warfarin, tacrolimus.	Conduction abnormalities, hypotension.	Avoid in patients with LV dysfunction. Diltiazem is contraindicated in patients taking ranolazine.	Abernethy DR, Schwartz JB: Calcium-antagonist drugs. N Engl J Med 1999;341:1447 1457.
Verapamil	20-35%	5 L/kg	90% ± 2%	Hepatic	4.5-12 hr	PO: (immediate release): 80-120 mg PO t.i.d. max dose 480 mg/days PO: (sustained release): 120-480 mg/day in 1-2 divided doses IV: (loading dose) 2.5-5 mg IV over 2-3 min, may repeat in 30 min with 5-10 mg if arrhythmia not suppressed. IC: 100-200 mcg for "no reflow" or "slow flow"	Inhibitor of CYP 3A4; leads to increases in concentrations of many drugs including alprazolam, carbamazepine, cyclosporine, dihydropyridine calcium channel blockers, HMG-CoA inhibitors, quinidine, warfarin, tacrolimus. May increase serum digoxin concentrations.	Conduction abnormalities, hypotension, constipation.	Avoid in patients with LV dysfunction. Verapamil is contraindicated in patients taking dofetilide. Verapamil is contraindicated in patients taking ranolazine.	

For abbreviations, see p. 864. For further discussion, see Chapter(s) 5-12, 19, 23.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
V. Oral Antiplatelet Drugs										
Aspirin	65-70%	0.15 ± 0.03 L/kg	49%	Hepatic	20 min (aspirin), 2.4 hr (salicylate)	Rapid platelet inhibition: chew and swallow 325 mg PO × 1 dose CAD (chronic therapy): 81-325 mg PO q.d.	NS	GI bleeding, dyspepsia, nausea, anaphylaxis (rarely), use cautiously in patients with asthma and nasal polyps.		Awtry EH, Loscalzo J: Aspirin. Circulation 2000; 101:1206-1218
Cilostazol	N/D	N/D	95-98%	Hepatic CYP3A4 and CYP2C19 (lesser extent)	11-13 h	100 mg PO b.i.d.	Cilostazol concentrations may be increased by CYP3A4 inhibitors including clarithromycin, diltiazem, erythromycin, fluconazole, fluoxetine, itraconazole, ketoconazole, verapamil and by CYP2C19 inhibitors, such as omeprazole.	Headache, diarrhea, dizziness, bleeding, palpitations, sinus tachycardia, rash	Cilostazol is contra-indicated in patients with CHF. Consider dose reduction to 50 mg PO b.i.d. in patients taking CYP3A4 or CYP2C19 inhibitors.	

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
V. Oral Antiplatelet Drugs—cont'd										
Clopidogrel	50%	ND	98%	Hepatic	8 hr (carboxylic acid derivative)	Prior to or at time of PCI: 300 mg-600 mg PO × 1 followed by 75 mg PO q.d. ACS: 300 mg PO × 1 followed by 75 mg PO q.d. Maintenance dose: 75 mg PO q.d.	NS	Rash, diarrhea, cases of thrombotic thrombocytopenic purpura have been reported. GI hemorrhage occurs less often than with aspirin.	Can be used in patients with an aspirin allergy. In the absence of a loading dose, takes 3-7 day for max platelet aggregation inhibition. If CABG planned, withhold for 5-7 days to minimize bleeding potential.	Quinn MJ, Fitzgerald DJ: Ticlopidine and clopidogrel. Circulation 1999; 100:1667-1672. Popma JJ, Berger P, Ohman EM, et al: Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126 (3 Suppl): 576s-599s.
Ticlopidine	80-90%	ND	98%	Hepatic	12.6 hr after single dose; 4-5 days with repeated dosing	Post–stent placement (ideally started at least 6-24 hr prior to procedure): 500 mg PO × 1, followed by 250 mg that evening and then 250 mg PO b.i.d. Maintenance dose: 250 mg PO b.i.d.	Ticlopidine may increase concentrations of carbamazepine, phenytoin, and theophylline	Neutropenia = 2.4%; severe neutropenia = 0.8%; thrombotic thrombocytopenic purpura, rash, diarrhea, nausea, bleeding, ↑ cholesterol, cholestatic jaundice, ↑ LFTs.	CBC q 2 wk for first 3 mo of therapy. Can be used in patients with an aspirin allergy.	Quinn MJ, Fitzgerald DJ: Ticlopidine and clopidogrel. Circulation 1999; 100:1667-72.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 5-12.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
VI. Glycoprotein (GB) IIb/IIIa Antagonists										
Abciximab	N/A	ND	ND	Proteolytic breakdown	10-30 min; remains in circulation for at least 21 days in a platelet-bound state	PCI: 0.25 mg/kg IV bolus over 5 min given 10-60 min prior to PCI, then 0.125 mcg/kg/min (max 10 mcg/min) IV infusion for 12 hr after PCI ACS (unresponsive to standard medical therapy in whom PCI is planned within 24 hr): 0.25 mg/kg IV bolus over 5 min, followed by a 10 mcg/min IV infusion for 18-24 hr prior to PCI and continued until 1 hr after PCI (see notes)	NS	Bleeding, profound, thrombocytopenia (platelets < 50,000) = 0.4-1.1%; obtain platelet count 2-4 hr after abciximab bolus and then daily.	In ACS, an infusion for 12 hr after PCI is recommended to maximize efficacy; 6% of patients develop human antichimeric antibodies.	Lincoff AM, Califf RM, Topol EJ: Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease. J Am Coll Cardiol 2000; 35:1103-15.
Eptifibatide	N/A	9.15 L	25%	Renal (50%)	2.5 hr	PCI (for patients with CrCl $\geq$ 50 mL/min): 180 mcg/kg bolus followed by CI of 2 mcg/kg/min and a second 180 mcg/kg bolus 10 min after the first bolus. A minimum of 12 hr of infusion is recommended. PCI (CrCl < 50 mL/min): 180 mcg/kg bolus followed by CI of 1 mcg/kg/min and a second 180 mcg/kg bolus 10 min after the first bolus. ACS (for patients with CrCl $\geq$ 50 mL/min): 180 mcg/kg bolus followed by CI of 2 mcg/kg/min ACS (CrCl < 50 mL/min): 180 mcg/kg bolus followed by CI of 1 mcg/kg/min.	NS	Bleeding, profound thrombocytopenia (platelets < 50,000) = 0-0.2%; obtain platelet count 6 hr after eptifibatide bolus and then daily.	Contra-indicated for patients on renal dialysis. Doses should be capped for patients weighing > 121 kg.	Lincoff AM, Califf RM, Topol EJ: Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease. J Am Coll Cardiol 2000; 35: 1103-5. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339: 436-43.

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Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
VI. Glycoprotein (GB) IIb/IIIa Antagonists—cont'd										
										The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): A randomized placebo-controlled trial. Lancet 2000;356: 2037-44.
Tirofiban	N/A	22-42 L	Minimal	Renal (65%)	1.5-3 hr	ACS: 0.4 mcg/kg/min for 30 min and then decreased to 0.1 mcg/kg/min continuing through angiography (if planned within 96 hr) and should conclude 12-24 hr after intervention Patients with CrCl < 30 mL/min should receive half the usual bolus and maintenance infusion rate (e.g., 0.2 mcg/kg/min for 30 min and then decreased to 0.05 mcg/kg/min)	NS	Bleeding, profound thrombocytopenia (platelets < 50,000) = 0.1-0.3%; obtain platelet count 6 hr after tirofiban bolus and then daily.		Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators: Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998;338: 1488-97.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 5-12.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
VII. Antithrombotic Agents										
Argatroban	N/A	0.174 L/kg	54%	Hepatic/ feces	40-50 min	HIT: 2 mcg/kg/min Cl. In patients with moderate hepatic impairment, reduce dose to 0.5 mcg/kg/min Cl	Combined use with warfarin can prolong INR	Bleeding, dyspnea, fever, hypotension, allergic reactions.	Check aPTT 2 hr into infusion and adjust infusion rate to achieve aPTT of 1.5-3 × baseline (not to exceed 100 s)	
Bivalirudin	N/A	ND	Not bound	Renal/ proteolysis	25 min	PCI in patients receiving provisional Gp IIb/IIIa inhibitor: 0.75 mg/kg bolus prior to PCI followed by 1.75 mg/kg/hr for the duration of procedure. The infusion may be continued for up to 4 hrs post PCI (optional). If needed, an infusion at a rate of 0.2 mg/kg/hr may then be initiated for up to 20 hr.	NS	Bleeding, back pain.	Dose reductions recommended for patients with CrCl < 30 mL/min	Lincoff MA, Bittl JA, Harrington RA, et al: Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289: 853-63.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
VII. Antithrombotic Agents—cont'd										
Dalteparin	87 ± 6% (SC)	0.04-0.06 L/kg	Minimal	Renal	1.8-2.4 hr (IV administration) 3-5 hr (SC administration)	DVT prophylaxis following abdominal surgery: 2500 IU (starting 1-2 hr prior to surgery) SC q.d. DVT prophylaxis following abdominal surgery (high-risk: 5000 IU starting the evening prior to surgery, followed by 5000 SC q.d. DVT prophylaxis following hip replacement: 2500 IU 2 hr prior to surgery, followed by 2500 IU 12 hr later and then 5000 IU SC q.d. DVT prophylaxis in medical patients with acute illness: 5000 IU SC q.d. DVT treatment: 200 IU/kg (max of 18,000 units) SC q.d. or 100 IU/kg (max of 10,000 units). SC q 12 hr (in patients of increased risk for bleeding) UA/NSTEMI: 120 IU/kg (max of 10,000 units) SC q 12 h for up to 6 days	NS	Bleeding, thrombocytopenia	aPTT is not followed for dosing adjustments. Use with caution in patients with CrCl < 30 mL/min. Avoid in patients with history of HIT-2.	Howard PA: Dalteparin: a low-molecular weight heparin. Ann Pharmacother 1997;31:192-203.

Enoxaparin	92% (SC)	0.12 L/kg	Minimal	Renal	5 hr	DVT prophylaxis following hip or knee replacement surgery: 30 mg SC q 12 hr started 12-24 hr postoperatively (if CrCl < 30 mL/min: 30 mg SC q.d.) DVT prophylaxis following abdominal surgery: 40 mg SC q.d., started 2 h prior to surgery (if CrCl < 30 mL/min: 30 mg SC q.d.) DVT prophylaxis in acutely ill medical patients: 40 mg SC q.d. (if CrCl < 30 mL/min: 30 mg SC q.d.) DVT/PE treatment: 1 mg/kg SC q 12 hr. 1.5 mg/kg SC q.d. can be used for treatment of DVT in inpatients (if CrCl < 30 mL/min: 1 mg/kg SC q.d.) UA/NSTEMI: 1 mg/kg SC q 12 hr × 48-96 hr or until the patient is stable (if CrCl < 30 mL/min: 1 mg/kg SC q.d.)	NS	Bleeding, thrombocytopenia.	aPTT is not followed for dosing adjustments. Avoid in patients with a history of HIT.	Petersen JL, Mahaffey KW, Hasselblad V, et al: Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: A systematic overview. JAMA 2004;292:89-96.
Fondaparinux	100% (SC)	7-11 L	94%	Renal	13-21 hr	DVT prophylaxis following surgery for hip fracture, knee or hip replacement: 2.5 mg SC q.d. beginning 6 to 8 hr post op after hemostasis is achieved. DVT & PE Treatment: 5 mg SC q.d. (weight < 50 kg); 7.5 mg SC q.d (50-100 kg); 10 mg SC q.d. (> 100kg) ACS: 2.5 mg SC q.d.	NS	Bleeding, thrombocytopenia, rash, no available antidote to reverse effects.	Contra-indicated in patients with CrCl < 30 mL/min aPTT not followed for dose adjustments	

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
VII. Antithrombotic Agents—cont'd										
Heparin (unfractionated)	10-30% (SC)	0.058 ± 0.011 L/kg	Extensive	Hepatic/ complex with antithrombin	30-150 min (dose depen-dent)	DVT prophylaxis: 5000-7500 units SC q 8-12 hr DVT and PE treatment: bolus dose of 70-80 U/kg, followed by continuous IV infusion of 15-18 U/kg/hr, titrated to an aPTT 1.5 to 2.5 times control value ST-elevation MI: (combination with alteplase, reteplase or tenecteplase) 60 U/kg (max 4000 units bolus at initiation of thrombolytic followed by 12 U/kg/hr (max 1000 units) Titrated to an aPTT of 50-70 sec and continued for 48 hr. UA/NSTEMI: 60 U/kg (max dose 4000 U) bolus followed by initial CI of 12 U/kg/hr (max 1000 U/hr). Titrated to an aPTT of 50-70 sec and continued for 48 hr PCI: bolus dose of 60-100 U/kg (max 10,000 units) prior to procedure, followed by incremental boluses to maintain ACT at 250-350 sec during the procedure PCI with glycoprotein IIb/IIIa inhibitor: bolus dose of 50-70 U/kg (max 7000 units) prior to procedure, followed by incremental boluses to maintain the ACT ⩾ 200 sec	NS	Bleeding, heparin-induced thrombocyto-penia, osteoporosis with long-term therapy, hyperkalemia (rarely).	To minimize bleeding risk, lower doses are recommended when given with fibrinolytics in the treatment of acute MI. aPTT measure-ments 6 hr after initiation of treatment or any dosage adjustment	Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. J Am Coll Cardial 2004;44:671-719. Hirsh J, Raschke R: Heparin and low-molecular-weight heparin: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126 (3 Suppl): 188S-203S.

Lepirudin	N/A	0.2 L/kg	<10%	Renal (45-48%)	1.3 hr, prolonged in RI	Heparin-induced thrombocytopenia (HIT) For patients with CrCl > 60 mL/min: loading dose of 0.4 mg/kg IV bolus (max 44 mg), followed by a CI of 0.15 mg/kg/hr (max 16.5 mg/hr) For patients with CrCl < 60 mL/min: loading dose = 0.2 mg/kg IV bolus Maintenance infusion in patients with renal insufficiency: CrCl 45-60 mL/min: infusion rate 0.075 mg/kg/hr CrCl 30-44 mL/min: infusion rate 0.045 mg/kg/hr CrCl 15-29 mL/min: infusion rate 0.0225 mg/kg/hr CrCl <15 mL/min: no infusion For patients with CrCl < 15 mL/min: additional bolus injections of 0.1 mg/kg every other day may be administered if aPTT falls below the therapeutic range	NS	Bleeding (major bleeding may occur more often than in heparin-treated patients), no available antidote to reverse effect, thrombocytopenia. Lower doses used if combined with thrombolytic therapy.	No cross-reactivity with heparin. aPTT monitored for dosing adjustments; titrate to aPTT of 1.5-2.5 × control. Antihirudin antibodies are commonly formed in patients who receive lepirudin for more than 6 days. Check aPTT 4 hr after start of therapy.	Greinacher A, Janssens U, Berg G, et al: Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. Circulation 1999; 100:587-93.

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Table A1–1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
VII. Antithrombotic Agents—cont'd										
Tinzaparin	87% (SC)	3.1-5 L/kg	Minimal	Renal	3-4 hr	DVT treatment with or without PE: 175 anti-Xa IU/kg SC q.d.	NS	Bleeding, thrombocytopenia.	aPTT is not followed for dosing adjustments. Use with caution in patients with CrCl < 30 mL/min. Avoid in patients with a history of HIT-2.	

For abbreviations, see p. 864. For further discussion, see Chapter(s) 5–12.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
VIII. Oral Anticoagulants										
Warfarin	≈100%	0.14 ± 0.06 L/kg	99%	CYP 3A4, 2C9, and 1A2	~37 hr	Individualize on the basis of concomitant disease states, medications, and dietary habits.	Effect increased by many drugs including amiodarone, azole antifungals, cimetidine, ciprofloxacin, clarithromycin, fluoxetine, fluvoxamine, fluvastatin, metronidazole, miconazole, nefazodone, protease inhibitors, trimethoprim-sulfamethoxazole, zafirlukast, zileuton Effect decreased by barbiturates, carbamazepine, cholestyramine, colestipol, dicloxacillin, griseofulvin, nafcillin, nevirapine, phenobarbital, phenytoin, rifabutin, rifampin.	Bleeding, skin necrosis, purple toe syndrome, alopecia, teratogenic.	Anti-thrombotic effect of warfarin is delayed for 72-96 hr.	Ansell J, Hirsch J, Poller L, et al: The pharmacology and management of the vitamin K antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126 (3 Suppl): 204S-33S.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 2, 5, 10, 11, 12, 24, 47.

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Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
IX. Thrombolytics										
Alteplase (tPA)	N/A	0.1 ± 0.01 L/kg	ND	Hepatic	5 min	ST-segment elevation MI: 15 mg IV bolus, followed by 0.75 mg/kg IV (up to 50 mg) over 30 min, followed by 0.5 mg/kg (up to 35 mg) over 60 min PE: 100 mg IV infusion over 2 hr Acute ischemic stroke: 0.9 mg/kg (maximum of 90 mg), give 10% initially as a bolus with the remainder given IV over 60 min	NS	Bleeding, intracranial hemorrhage.	To minimize bleeding, low-dose, weight-adjusted unfrac-tionated heparin should be used when administered with a fibrinolytic (see heparin).	The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
Anistreplase	N/A	0.084 ± 0.027 L/kg	ND	Hepatic	1.2 ± 0.4 hr	ST-segment elevation MI: 30 U IV over 2-5 min	NS	Bleeding, intracranial hemorrhage, allergic reactions (similar to streptokinase).	Adjunct IV heparin is associated with increased bleeding and no improve-ment in outcome; therefore, reserve for patients at high risk or systemic or venous thrombo-embolism. If indicated, without a bolus, 6 hr after anistreplase, once aPTT is less than twice control value. Same allergic profile as streptokinase.	

Reteplase (rPA)	N/A	6 L	ND	Hepatic/ renal	13-16 min	ST-segment elevation MI: 10 units IV over 2 min, repeat × 1 dose in 30 min	NS	Bleeding, intracranial hemorrhage.		Martin U, Von Molendorff E, Akpan W: Pharmacokinetic and hemostatic properties of recombinant plasminogen activator BM 06.022 in healthy volunteers. Thromb Haemost 1991;66:569-74. The GUSTO-III Investigators: A comparison of reteplase with alteplase for acute myocardial infarction. N Engl J Med 1997;337: 1118-23.

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Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
IX. Thrombolytics—cont'd										
Streptokinase	N/A	0.08 ± 0.04 L/kg	ND	Reticuloendothelial system	83 min	ST-segment elevation MI: 1.5 MU IV over 60 min PE/DVT: 250,000 units IV over 30 min, followed by 100,000 U/hr for 24-72 hr Thrombosis: 250,000 units IV over 30 min, followed by 100,000 U/hr for 72 hr	N/A	Bleeding, intracranial hemorrhage. hypotension, allergic reactions.	If indicated, heparin is initiated without a bolus, 6 hr after the infusion of streptokinase once aPTT is less than twice control value. Use with caution in patients with previous exposure to streptokinase or anistreplase or recent streptococcal infection. Slowing the rate of infusion may minimize hypotension.	The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.

Tenecteplase	N/A	~Plasma volume	ND	Hepatic	Biphasic: initial = 20 min, terminal = 90-130 min	ST-segment elevation MI: IV bolus over 5-10 sec. Weight-based dosing: 30 mg if < 60 kg, 35 mg if 60-69 kg, 40 mg if 70-79 kg, 45 mg if 80-89 kg, 50 mg if ⩾ 90 kg. Total dose should not exceed 50 mg	NS	Bleeding (may cause fewer noncerebral bleeds and need for transfusion compared with alteplase), intracranial hemorrhage.		Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators: Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. Lancet 1999;354:716-22.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 5, 11.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
X. Cardiac Glycosides										
Digoxin	~80% (tablets, elixir) ~100% (capsules)	5.6 L/kg	25 ± 5%	~85% renal, minor hepatic metabolism and intestinal degradation	For CrCl > 60 mL/min: 1.5 days 30 mL/min: 2 days 15 mL/min: 3 days < 10 mL/min: > 4 days	Loading dose (PO or IV) 10 mcg/kg LBW Loading dose ESRD (PO or IV): 7 mcg/kg LBW Administer $^1/_2$ loading dose initially, then $^1/_4$ q 6 hr × 2 Maintenance dose: % lost per day × loading dose where % lost per day = (CrCl/5 + 14) ÷ 100 Serum drug concentration: 0.5-1 ng/mL (heart failure)	Digoxin concentrations increased by amiodarone, carvedilol, clarithromycin, cyclosporine, erythromycin, itraconazole, ketoconazole, propafenone, quinidine, ranolazine tacrolimus, telmisartan, verapamil. Digoxin concentrations reduced by concomitant administration with cholestyramine, St. John's wort, colestipol.	Arrhythmias, anorexia, nausea, vomiting, weakness, lethargy, blurred vision, hallucinations.	Obtain blood samples for digoxin concentration at least 6 hr after an oral dose; 4 hr for IV dose. Hypokalemia, hypomagnesemia, and hypercalcemia increase likelihood of digoxin toxicity.	Hauptman PJ, Kelly RA: Digitalis. Circulation 1999;99: 1265-70.
Digoxin Immune Fab	N/A	0.46 L/kg	ND	Renal	16-20 hr in normal renal function	1. Calculate total body stores (TBS) of digoxin If serum digoxin concentration (SDC) available, total body stores = TBS (mg) = $\frac{(\text{SDC ng/mL}) \times (5.6\ \text{L/kg}) \times (\text{weight kg})}{1000}$ For a known ingestion of digoxin. TBS = (mg of digoxin ingested) (0.8); use 1.0 for capsules 2. Calculate number of vials of digoxin immune Fab: # of vials needed = $\frac{\text{TBS (mg)}}{0.6\ \text{mg/vial}}$	NS	Allergic reactions, hypokalemia	Except in pediatrics, round dosage up to the next whole vial. Reconstitute powder with 4 mL sterile water prior to injection. Before full neutralizing dose, a test dose of 1 mg IV is recommended to be given through a 0.22 micron filter.	Antman EM, Wenger TL, Butler VP Jr, et al: Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. Circulation 1990; 81:1744-52.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 2, 14, 19, 24.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XI. Angiotensin-Converting Enzyme Inhibitors										
Benazepril	> 37%	0.12 L/kg	97%	Renal	10-11 hr (For active drug)	5-80 mg/day in 1-2 divided doses	May increase serum lithium levels.	Hypokalemia, hypotension, cough, worsening, renal function, angioedema, fetal abnormalities, dysgeusia, neutropenia (captopril), rash (captopril).		
Captopril	75-91%	0.81 ± 0.18 L/kg	30%	Renal	1.7 hr	25-300 mg/day in 2-3 divided doses	May increase serum lithium levels.		Should be taken on empty stomach to increase absorption.	
Enalapril	60%	1.7 ± 0.7 L/kg	<50%	Renal	11 hr (active drug)	PO: 2.5-40 mg/day in 1-2 divided doses IV: 0.625-1.25 mg IV q 6 hr initially, up to 5 mg IV q 6 hr	May increase serum lithium levels.		For IV dosing, start with 0.625 mg if patient is taking a diuretic.	
Fosinopril	36%	0.13 ± 0.03 L/kg	>95%	Hepatic/ renal	12 hr (active drug)	10-80 mg/day in 1-2 divided doses	May increase serum lithium levels.			
Lisinopril	6-60%	2.4 ± 1.4 L/kg	Negli-gible	Renal	12 hr	2.5-40 mg per day	May increase serum lithium levels.			
Moexipril	13%	180 L	50-70%	Renal/fecal	2-9 hr (active drug)	7.5-30 mg/day in 1-2 divided doses	May increase serum lithium levels.		Should be taken on empty stomach to increase absorption.	
Perindopril	20-30%	0.22 L/kg	10-20%	Hepatic/ renal	25-40 hr (active drug)	2-16 mg/day in 1-2 divided doses Max dose of 8 mg/day in elderly patients	May increase serum lithium levels.			Todd PA, Fitton A: Perindopril: a review of its pharmacological properties and therapeutic use in cardiovascular disorders. Drugs 1991;42:90-114.

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Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XI. Angiotensin-Converting Enzyme Inhibitors—cont'd										
Quinapril	>60%	0.4 L/kg	97%	Renal	1.9-2.5hr, 25 hr terminal	5-80 mg/day in 1-2 divided doses	May increase serum lithium levels.	Hypokalemia, hypotension, cough, worsening, renal function, angioedema fetal abnormalities, dysgeusia, neutropenia (captopril), rash (captopril).		
Ramipril	50-60%	ND	56%	Renal	Triphasic, 4 hr, 9-18 hr, >50 hr	1.25-20 mg/day in 1-2 divided doses	May increase serum lithium levels.			
Trandolapril	70%	18 L	80%	Hepatic/renal	15-24 hr (active drug)	1-8 mg/day in 1-2 divided doses	May increase serum lithium levels.			

Reference for angiotensin-converting enzyme section: Brown NJ, Vaughan DE: Angiotensin-converting enzyme inhibitors. Circulation 1998;97:1411-20.
For abbreviations, see p. 864. For further discussion, see Chapter(s) 5, 14, 30.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XII. Angiotensin Receptor Antagonists										
Candesartan	42%	0.13 L/kg	>99%	Renal/bile	9 hr	HTN: 4-32 mg PO q.d. CHF: 4 mg PO q.d. to start titrating every 2 weeks to a target dose of 32 mg PO q.d.	NS	Hypokalemia, hypotension, worsening renal function, angioedema, fetal abnormalities. Use cautiously in patients with a history of angioedema due to ACE inhibitor.		Song JC, White CM: Pharmacologic, pharmacokinetic, and therapeutic differences among angiotensin II receptor antagonists. Pharmacotherapy 2000;20:130-9. Burnier M, Brunner HR: Angiotensin II receptor antagonists. Lancet 2000;355:637-45.
Eprosartan	15%	308 L	98%	Bile	5-7 hr	400-1200 mg/day in 1-2 divided doses	NS			
Irbesartan	70%	53-93 L	90%	Bile	11-15 hr	75-300 mg PO q.d.	NS			
Losartan	33%	34 L (losartan) 12 L (active metabolite)	98%	Hepatic (CYP 2C9 and 3A4) of parent compound to active metabolite	2 hr (losartan) 6-9 hr (active metabolite)	25-100 mg PO q.d.	Fluconazole and rifampin can attenuate blood pressure-lowering effects of losartan.		Reduce initial dose by 50% for patients with hepatic failure.	
Olmesartan	26%	17 L	99%	Renal/Bile	12-18 hr	10-40 mg PO q.d.	NS			
Telmisartan	43%	500 L	99.5%	Hepatic	24 hr	20-80 mg PO q.d.	Telmisartan can increase serum digoxin concentrations.			
Valsartan	25%	17 L	95%	Hepatic	9 hr	HTN: 80-320 mg PO q.d. CHF: 40 mg PO b.i.d. to start titrated to 160 mg PO b.i.d.	NS			

For abbreviations, see p. 846. For further discussion, see Chapter(s) 5, 14, 30.

Continued

Table A1–1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XIII. Loop Diuretics										
Bumetanide	80-100%	13-25 L/kg	95%	Hepatic/ renal	1 hr (normal), 1.6 hr (RI), 2.3 hr (cirrhosis)	PO/IV: 0.5-10 mg/day in 2-3 divided doses IV infusion: 1 mg IV loading dose followed by 0.5-1 mg/hr	May increase serum lithium concentrations.	Hypokalemia, hypomagnesemia, hypocalcemia, orthostatic hypotension, interstitial nephritis, ototoxicity, hyperuricemia.	For normal renal function, 1 mg bumetanide = 40 mg IV furosemide.	Brater DC: Diuretic therapy. N Engl J Med 1998;339:387-95.
Ethacrynic Acid	100%	ND	>90%	Hepatic/ renal	2-4 hr	PO: 25-100 mg/day in 2-3 divided doses, maximum dose = 200 mg b.i.d. IV: 0.5-1 mg/kg/dose (maximum 100 mg/dose)			Nonsulfonamide; reserve for patients with severe sulfa allergy. Higher rates of ototoxicity compared with other loop diuretics.	
Furosemide	40-70%	0.2 L/kg	>98%	Renal/ hepatic	1.5-2 hr increased in patients with CHF, RI, and cirrhosis	PO: 20-320 mg/day in 2-3 divided doses IV: maximum IV bolus dose = 200 mg IV infusion: 40 mg IV loading dose followed by 10-40 mg/hr			IV dose is usually 50% of PO dose. For IV bolus dose ⩾ 120 mg, max infusion rate of 4 mg/min.	
Torsemide	80-100%	0.14-0.19 L/kg	98%	Hepatic/ renal	3-4 hr, prolonged in CHF and RI	PO/IV: 5-20 mg/day to start; dosage can be doubled to response or maximum of 200 mg/day IV infusion: 20 mg IV loading dose followed by 5-20 mg/hr			20 mg torsemide = 40 mg IV furosemide.	

For abbreviations, see p. 864. For further discussion, see Chapter(s) 14, 30.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XIV. Inotropes										
Inamrinone (previously called amrinone)	N/A	1.8 ± 0.9 L/kg	20-50%	Hepatic/ renal	4-6 hr, prolonged in RI and CHF	0.75 mg/kg IV loading dose over 2-3 min, maintenance dose of 5-20 mcg/kg/min	NS	Thrombocytopenia (occurs more often than with milrinone therapy, platelet counts generally return to baseline 2-4 days after discontinuing therapy); arrhythmias, fever.		Rocci ML, Wilson H: The pharmacokinetics and pharmacodynamics of newer inotropic agents. Clin Pharmacokinet 1987;13: 91-109.
Dobutamide	N/A	0.2 ± 0.08 L/kg	ND	Hepatic	2 min	2.5-30 mcg/kg/min	Avoid MAO inhibitors.	Arrhythmias, hypokalemia, angina, palpitations, tremor.		
Dopamine	N/A	1.8–2.45 L/kg	ND	Hepatic/ renal/tissue	2 min	1-2 mcg/kg/min = predominant dopamine receptor agonist 2-5 mcg/kg/min = predominant β-agonist > 5 mcg/kg/min = α- and β-agonist > 10 mcg/kg/min = predominant α-agonist	Avoid MAO inhibitors.	Arrhythmias, hypertension, angina, decreased peripheral perfusion, painful extravasation.		
Isoproterenol	N/A	ND	ND	Hepatic/ renal	2.5-5 min	2-20 mcg/min	NS	Hypotension, arrhythmias, hypokalemia.		

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XIV. Inotropes—cont'd										
Milrinone	N/A	0.3–0.47 L/kg	70%	Renal	1.5-2 hr increases to 4 + hr in RI	Optional loading dose 50 mcg/kg IV over 10-20 min, maintenance dose is 0.25-0.75 mcg/kg/min	NS	Arrhythmias, hypotension, decreased incidence of thrombocytopenia compared with inamrinone.	Recommended initial infusion rates for patients with RI: CrCl 41-50 mL/min: 0.43 mcg/kg/min and titrate to effect CrCl 31-40 mL/min: 0.38 mcg/kg/min and titrate to effect CrCl 21-30 mL/min: 0.33 mcg/kg/min and titrate to effect CrCl 11-20 mL/min: 0.28 mcg/kg/min and titrate to effect CrCl 6-10 mL/min: 0.23 mcg/kg/min and titrate to effect CrCl <5 mL/min: 0.2 mcg/kg/min and titrate to effect	Benotti JR, Lesko LJ, McCue JE, et al: Pharmacokinetics and pharmacodynamics of milrinone in chronic congestive heart failure. Am J Cardiol 1985;56:685-9.

For abbreviations, see p. 864. For further discussion, see Chapter 17.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XV. Antiarrhythmic Agents										
Adenosine	N/A	ND	ND	Cellular uptake and degradation	<10 sec	6 mg IV over 1-2 sec, if ineffective 12 mg can be given 2 min later and repeated again if necessary	Dipyridamole enhances pharmacologic effect of adenosine. Theophylline and caffeine inhibit the therapeutic actions of adenosine.	Chest discomfort, dyspnea, flushing, headache.		
Amiodarone	50%	66 L/kg	96%	Hepatic	~50 days	Atrial fibrillation (oral): 600-1200 mg/day × 1-2 wk, then 400 mg/day × 1 mo then 200 mg/day Ventricular arrhythmias (oral): 800-1600 mg/day × 1-3 wk, then 600-800 mg/day × 1 mo, then 400 mg/day VT: 150 mg IV over 10 min followed by 1 mg/min IV CI for 6 hr followed by 0.5 mg/min thereafter. Additional 150-mg doses can be given for recurrent arrhythmias. VF (pulseless VT): 300 mg IV bolus. If VF/pulseless VT recurs, consider administration of a second dose of 150 mg. IV infusion may be used with dosing as provided earlier. Serum drug concentration: 0.5-2.5 mcg/mL, although not well correlated with therapeutic or toxic effects.	Potent inhibitor of CYP P450 enzymes, increase concentrations of many drugs including alprazolam, carbamazepine, cyclosporine, dihydropyridine calcium channel blockers, digoxin, HMG-CoA inhibitors (atorvastatin, lovastatin, simvastatin), phenytoin, procainamide, quinidine, tacrolimus, triazolam, and warfarin.	Hypersensitivity pneumonitis, pulmonary alveolitis, sinus bradycardia, conduction abnormalities, ↑ QT interval, torsades de pointes (<1%), thyroid abnormalities, corneal deposits, optic neuritis, tremor, ataxia, peripheral neuropathy, blue-gray skin discoloration, photosensitivity, nausea, ↓ appetite, ↑ LFT.	Maximum IV daily dose = 2000 mg.	Hilleman D, Miller MA, Parker R, et al: Optimal management of amiodarone therapy: Efficacy and side effects. Pharmacotherapy 1998;18:138S-45S.
Disopyramide	80-90%	1.4-1.7 L/kg	50-65%	Renal/ hepatic (CYP 3A4)	6-9 hr, 12-43 hr in RI	Immediate release: Initially 150 mg PO q 6 hr (150 mg PO q 12 hr in moderate RI; 150 mg q 24 hr in severe RI), then increase to 200-300 mg PO q 6 hr (150-300 mg q 12-24 hr in RI) Serum drug concentration: 3-6 mcg/mL	Effects of disopyramide may be increased in patients receiving drugs that inhibit CYP 3A4. Effects of disopyramide may be decreased in patients receiving drugs that are inducers of CYP 3A4.	Anticholinergic (dry mouth, urinary retention, constipation, blurred vision), exacerbation of CHF, QT prolongation, bradycardia, conduction abnormalities.	To convert to the sustained-release product: divide the total daily dose of immediate release product by 2 and give q 12 hr.	

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XV. Antiarrhythmic Agents—cont'd										
Dofetilide	~90	~3 L/kg	64%	Renal/hepatic (CYP 3A4)	8 hr	Patients with a CrCl >60 mL/min should receive a one-time 500 mcg dose. 2-3 hr after administering the dose, the patient's QTc should be measured. If no significant QTc prolongation is observed, the drug should be continued at 500 mcg PO b.i.d. If QTc increases by > 15% or if QTc exceeds 500 msec, (550 msec in patients with ventricular conduction abnormalities) the drug should be administered at 250 mcg PO b.i.d. CrCl (mL/min) 40-60: starting dose = 250 mcg PO b.i.d. If QTc increases by > 15% or exceeds 500 msec (550 msec in patients with ventricular conduction abnormalities) (after first dose), adjust dose to 125 mcg PO b.i.d. CrCl (mL/min) 20-39: starting dose = 125 mcg PO b.i.d. If QTc increases by >15% or exceeds 500 msec (550 msec in patients with ventricular conduction abnormalities) (after first dose), adjust dose to 125 mcg PO q.d. See notes for additional dosing/monitoring information.	Contraindicated with cimetidine, ketoconazole, megestrol acetate, prochlorperazine, trimethoprim, and verapamil secondary to inhibition of dofetilide tubular secretion. Contraindications with hydrochloro-thiazide due to risk of increased dofetilide concentrations and prolonged QTc. Amiodarone: Patients previously receiving amiodarone may be changed to dofetilide when amiodarone has been discontinued for 3 mo or there is documentation of an amiodarone serum concentration <0.3 mcg/mL. Class I or class III antiarrhythmics (excluding amiodarone): Dofetilide should not be started until 3 half-lives of the previous medication have passed. Avoid inhibitors of CYP 3A4.	Torsades de pointes (3%), dofetilide is contraindicated in patients with CrCl <20 mL/min or if base line QTc exceeds 440 ms (or if baseline QTc >500 msec in patients with ventricular conduction abnormalities)	When starting therapy or increasing dose, patients need to be hospitalized for at least 3 days for continuous ECG monitoring. With each succeeding dose during hospitalization, the patient's QTc should be measured 2-3 hr after drug administration. If at any point after the second dose the patient's QTc >500 msec (or if QTc >550 msec in patients with ventricular conduction abnormalities), dofetilide therapy should be terminated.	Kalus JS, Mauro VF: Dofetilide: A class III-specific antiarrhythmic agent. Ann Pharmacother 2000;34:44-56.

Flecainide	95%	8-10 L/kg	30-40%	Hepatic (CYP 2D6)/ renal	7-23 hr, may be pro-longed to 60 hr in elderly people, CHF, hepatic disease, or severe RI	Initially, 50-100 mg PO q 12 hr (50-100 mg PO q 24 hr in elderly, CHF, hepatic disease, or severe RI) and increase dose by 50-100 mg/day q 3-7 day depending on ECG findings. Max dose = 300-400 mg/day Serum drug concentration: 0.2-1 mcg/mL	Flecainide concentrations may be increased by the following drugs: amiodarone, cimetidine, fluoxetine haloperidol, paroxetine, quinidine, and ritonavir. Flecainide may increase serum digoxin concentrations.	Dizziness, visual disturbances, headache, proarrhythmic activity.		
Ibutilide	N/A	11 ± 4 L/kg	40%	Hepatic	6 hr	1 mg IV over 10 min (0.01 mg/kg for patients < 60 kg). Dose may be repeated in 10 min if no response	NS	Nausea, ↑ QT interval, torsades de pointes (1.7%); incidence of torsades de pointes may be increased in patients with CHF.	Patient should be monitored for pro-arrhythmias for at least 4 hr after a dose is given.	Cropp JS, Antal EG, Talbert RI: Ibutilide: A new class III antiarrhythmic agent. Pharmacotherapy 1997;17:1-9.
Lidocaine	N/A	1.1 L/kg (reduced in CHF and hepatic disease)	60-80%	Hepatic (CYP 3A4)	1.5-2 hr, 4-12 hr with cirrhosis or CHF	75 mg IV loading dose followed by 50 mg IV q 5 min × 3 (total dose 225 mg). Decrease loading dose for CHF or hepatic dysfunction. Infusion of 2 mg/min (1 mg/min in patients with moderate LVD, 0.5 mg/min in patients with shock, severe LVD, or significant hepatic dysfunction) Serum drug concentration: 2-5 mcg/mL	Drugs that inhibit CYP 3A4 may increase the effects of lidocaine.	Bradycardia, conduction abnormalities, dizziness, drowsiness, paresthesias, muscle twitching, confusion, vertigo, seizures (neurologic adverse effects are concentration related).		

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XV. Antiarrhythmic Agents—cont'd										
Mexiletine	90%	6.6-10.8 L/kg	70%	Hepatic (CYP 2D6)	8-15 hr	Initially, 200 mg PO q 8 hr and increase dose q 1-3 day by 50 mg q 8 hr. Max dose = 900-1200 mg/day Serum drug concentration: Not well correlated with therapeutic or toxic effects	Mexiletine concentrations may be increased by the following drugs: amiodarone, cimetidine, fluoxetine, haloperidol, paroxetine, quinidine, and ritonavir.	Tremor, ataxia, confusion, paresthesias, rarely psychosis or seizures, proarrhythmic activity.	Take with food or antacid to reduce GI distress.	
Moricizine	35-45%	5.9-11.6 L/kg	95%	Hepatic/ renal	3-4 hr, in-creased in RI	Initially 200 mg PO q 8 hr and increase dose in 3- to 5-day intervals to 250 mg PO q 8 hr, then 300 mg PO q 8 hr depending on ECG changes and side effects Serum drug concentration: Not well correlated with therapeutic or toxic effects	May decrease theophylline concentrations. Cimetidine may increase moricizine concentrations.	Nausea, anorexia, dizziness, proarrhythmic activity, worsening of baseline conduction disturbances.		
Procainamide	70-85%	2.5 L/kg	15-25%	Renal/hepatic (active metabolite, NAPA–primarily renally eliminated)	Procain-amide: 4 hr (no RI), 8-24 hr (RI) NAPA: 8 hr (no RI), 12-70 hr (RI)	(IV/PO): Loading dose: no RI: 17 mg/kg, mild RI: 15 mg/kg, severe RI (CrCl <20 mL/min): 13 mg/kg Maintenance dose: no RI: 3 mg/kg/hr mild RI: 2 mg/kg hr severe RI (CrCl <20 mL/min): 1 mg/kg/hr Serum drug concentration: 4-10 mcg/mL (procainamide); <25 mcg/mL (NAPA)	Procainamide concentrations may be increased by the following drugs: amiodarone, cimetidine, ranitidine, trimethoprim.	Hypotension (parenteral administration), ↑QT interval, torsades de pointes, ↑QRS, ↑PR, drug-induced lupus.	Dose is based on total body weight. Infuse loading dose over 30-60 min. When converting IV to PO, stop IV infusion 4 hr after first oral sustained-release dose.	Nolan PE: Pharmacokinetics and pharmaco-dynamics of intravenous agents for ventricular arrhythymias. Pharmacotherapy 1997;17:65S-75S.
Propafenone	25-75%	3.6 ± 2.6 L/kg	85-95%	Hepatic (CYP 1A2, 2D6, 3A4)	2-32 hr	Extended-release capsule: Initiate with 225 mg PO q 12 hr and increase dose in 5-day intervals to 325 mg q 12 hr then 425 mg q 12 hr depending on ECG. 150 mg PO q 8 hr and increase dose in 3- to 5-day intervals to 225 mg PO q 8 hr then 300 mg PO q 8 hr depending on ECG changes Serum drug concentration: Not well correlated with therapeutic or toxic effects	May decrease the metabolism of warfarin (monitor) INR); may increase serum digoxin concentrations	Metallic taste, dizziness, worsening of asthma, proarrhythmic activity, syndrome of inappropriate antidiuretic hormone.	150 mg q 8 hr of immediate release tablets produces similar con-centrations as 325 mg q 12 of sustained release capsules	

Quinidine	60-80%	2.7 ± 1.2 L/kg (reduced in HF)	80%	Hepatic (CYP 3A4)/ renal	6 hr (increases up to 12 hr in elderly patients and those with hepatic disease)	Maintenance Sulfate (IR): ≤65 y: 600 mg PO q 6 hr >65 y: 300 mg PO q 6 hr severe renal impairment: 200 mg PO q 8 hr Sulfate (SR): ≤65 y: 600 mg PO q 8 hr >65 y: 300 mg PO q 8 hr severe renal impairment: 300 mg PO q 12 hr Gluconate (SR) ≤65y: 648 mg PO q 8 hr >65 y: 324 mg PO q 8 hr severe renal impairment: 324 mg PO q 12 hr Serum drug concentration: 2-6 mcg/mL	Quinidine is an inhibitor of CYP 2D6 and may increase the effect of the following drugs: amitryptyline, clozapine, codeine, desipramine, doxepin, fluoxetine haloperidol, imipramine, meperidine, metoprolol, morphine, oxycodone, paroxetine, perphenazine, propranolol, risperidone, thioridazine, tramadol, trazodone, and venlafaxine. Quinidine may increase digoxin and amiodarone concentrations. Drugs that inhibit CYP 3A4 may increase the effects of quinidine.	Cinchonism, ↑ QR interval, torsades de pointes, drug fever, pruritus, rash, thrombocytopenia.		Grace AA, Camm AJ: Quinidine. N Engl J Med 1998;338:35-44.

Continued

Table A1–1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XV. Antiarrhythmic Agents—cont'd										
Sotalol	90-100%	1.2-2.4 L/kg	Not bound	Renal	8-20 hr (up to 40 hr in severe RI)	Atrial fibrillation or atrial flutter: patients should be in a monitored setting for a min of 3 day on their maintenance dose, 80 mg PO b.i.d. (80 mg PO q.d., if CrCl = 40-60 mL/min). QT interval should be checked 2-4 hr after each dose. If the QTc is <500 msec after the patient has received 5-6 doses, then the patient can be discharged. Alternatively during hospitalization, the dose can be increased to 120 mg PO b.i.d. (120 mg PO q.d. if CrCl = 40-60 mL/min) and the patient followed for 5-6 doses. Max dose = 160 mg PO b.i.d. (160 mg PO q.d. if CrCl = 40-60 mL/min). Ventricular arrhythmias: During initiation and titration QT interval should be monitored 2-4 hr after each dose. Patients should be in a monitored setting for at least 3 days (or 5-6 doses if dosing is once daily) after dosage titration. 80 mg PO b.i.d initially (80 mg PO q.d if CrCl 30-60 mL/min). If necessary, the dose may be increased to 240-320 mg/day (120-160 mg/day if CrCl 30-60 mL/min). Doses as high as 480-640 mg/day should only be used when potential benefit outweighs risk of adverse events.	NS	Bradycardia, conduction disturbances, bronchospasm, exacerbation of CHF, ↑ QT interval, torsades de pointes.	Use for atrial arrhythmias is contraindicated in patients with CrCl <40 mL/min or in patients with baseline QTc interval >450 msec. When sotalol is being used for atrial arrhythmias, dose should be decreased or the drug discontinued if the QTc prolongs to ≥ 500 msec. When being used for ventricular arrhythmias, the sotalol dose should be decreased or the drug discontinued if the QTc prolongs to ≥ 550 msec. Most cases of torsades de pointes occur within 3 days of initiating therapy; incidence of torsades de pointes is dose related.	Bauman JL: Class III antiarrhythmic agents: The next wave. Pharmacotherapy 1997;17:76S-83S.

Reference for antiarrhythmic agents section: Kowey PR: Pharmacological effects of antiarrhythmic drugs. Review and update. Arch Intern Med 1998;158:325-32.
For abbreviations, see p. 864. For further discussion, see Chapter 19.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XVI. HMG-CoA Reductase Inhibitors										
Atorvastatin	12%	381 L	98%	Hepatic (CYP 3A4)	14 hr	10-80 mg PO q.d.	Serum concentrations of atorvastatin, lovastatin, and simvastatin may be ***increased*** by the following drugs: amiodarone, cimetidine, clarithromycin, cyclosporine, delavirdine, diltiazem, erythromycin, fluoxetine, fluconazole, fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ranolazine, ritonavir, saquinavir, tacrolimus, verapamil, zafirlukast. Serum concentrations of atorvastatin, cerivastatin, lovastatin, and simvastatin may be ***decreased*** by the following drugs: barbiturates, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin.	Gastrointestinal upset, headaches, myalgias, ↑ creatine kinase, ↑ LFTs, rash, insomnia, nightmares. Contraindicated in pregnancy and in nursing mothers.	Can be taken any time of day because of long half-life.	
Lovastatin	5%	ND	>95%	Hepatic (CYP 3A4)	2 hr	10-80 mg daily (in 1-2 divided doses)			Bioavailability increased by administration with food; take with evening meal. Dose should not exceed 20 mg/day in patients taking fibric acid derivatives, niacin, or cyclosporine. Dose should not exceed 40 mg/day in patients taking amiodarone or verapamil.	Knopp RH: Drug treatment of lipid disorders. N Engl J Med 1999;341:498-511.
Simvastatin	5%	ND	95%	Hepatic (CYP 3A4)	1-2 hr	5-80 mg PO q.d.			Take in the evening. In patients taking gemfibrozil or cyclosporine, the simvastatin dose should not exceed 10 mg/day. In patients	

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XVI. HMG-CoA Reductase Inhibitors—cont'd										
									taking amiodarone or verapamil the simvastatin dose should not exceed 20 mg/day.	
Pravastatin	17%	0.46 L/kg	43-55%	Hepatic (sulfation)	1-2 hr	10-40 mg PO q.d.	NS	Gastrointestinal upset, headaches, myalgias, ↑ creatine kinase, ↑ LFTs, rash, insomnia, nightmares. Contraindicated in pregnancy and in nursing mothers.	Take in the evening. Food decreases absorption.	Knopp RH: Drug treatment of lipid disorders. N Engl J Med 1999; 341:498-511.
Fluvastatin	20-30%	0.42 L/kg	98%	Hepatic (CYP 2C9)	1.2 hr	Immediate release: 20-80 mg/day in 1-2 divided doses Extended release: 80 mg PO q.d.	Serum concentrations of fluvastatin may be increased by the following drugs: amiodarone, cimetidine, fluconazole, fluoxetine, fluvoxamine, itraconazole, ketoconazole, metronidazole, ticlopidine, zafirlukast. Serum concentrations of fluvastatin may be decreased by the following drugs: barbiturates, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin. Fluvastatin may increase the effect of warfarin.		Take in the evening.	

Rosuvastatin	20%	134 L	88%	Feces	19 hr	5-40 mg PO q.d.	Rosuvastatin concentrations may be increased by cyclosporine, gemfibrozil, and itraconazole. Rosuvastatin absorption may be decreased by antacids (administer rosuvastatin at least 2 hr before antacid) Rosuvastatin may increase the effect of warfarin	Same clinical cautions as listed for other HMG CoA reductase inhibitors.	Consider 5 mg PO q.d. as initial dose in Asian patients and patients with CrCl <30 mL/min. Dose should not exceed 10 mg/day for patients taking gemfibrozil. Dose should not exceed 5 mg/day for patients taking cyclosporine.	

For abbreviations, see p. 864. For further discussion, see Chapter(s) 26, 27.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XVII. Bile Resins										
Cholestyramine	Not absorbed from GI tract	N/A	N/A	Feces	N/A	4-16 g/day in 1-4 divided doses (max = 24 g/day)	Binds numerous medications. Resins should be administered at least 2 hr before or 6 hr after warfarin, theophylline, digoxin levothyroxine, and HMG-CoA reductase inhibitors.	Constipation, bloating, flatulence, impaired absorption of fat-soluble vitamins, ↑ triglycerides.	Mix each packet or scoop with 2-6 oz fluid.	Knoop RH: Drug treatment of lipid disorders. N Engl J Med 1999;341:498-511.
Colestipol	Not absorbed from GI tract	N/A	N/A	Feces	N/A	Granules: 5 g b.i.d. initially, increasing to a max of 30 g/day in 1-4 divided doses Tablets: 2 g b.i.d. initially, increasing to a max of 16 g/day in 1-4 divided doses			Mix granules with 2-6 oz fluid.	
Colesevelam	Not absorbed from GI tract	N/A	N/A	Feces	N/A	1.9 g (3 tabs) PO b.i.d. or 3.8 g (6 tabs) PO q.d. (max = 7 tabs/day)	Colesevelam may reduce verapamil concentrations. Colesevelam may be administered concurrently with HMG-CoA reductase inhibitors.	Constipation and dyspepsia. May impair vitamin K absorption	Take each dose with a meal.	

For abbreviations, see p. 864. For further discussion, see Chapter(s) 26, 27.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XVIII. Fibric Acid Derivatives										
Fenofibrate	60-90%	0.9 L/kg	>99%	Renal	20 hr (prolonged with renal dysfunction)	Tablet (Tricor): 48 mg PO q.d. to start maximum dose = 145 mg/day Tablet (Triglide™): 50 mg PO q.d. to start maximum dose = 160 mg/day Micronized capsule (Lofibra): 67 mg PO q.d. to start maximum dose = 200 mg/day (take with meal) Micronized capsule (Antara): 43 mg PO q.d. to start maximum dose = 130 mg/day (take with meal)	Risk of myopathy is increased when administered concomitantly with HMG-CoA reductase inhibitors. May increase the effects of warfarin through protein binding displacement.	Dyspepsia, abdominal pain, diarrhea, cholelithiasis, ↑ LFTs. Use with caution if CrCl < 50 mL/min.	Absorption is increased when taken with food.	Balfour JA, McTavish D, Heel RC: Fenofibrate: A review of its pharmaco-dynamic dynamic and pharmacokinetic properties and therapeutic use in dyslipidaemia. Drugs 1990;40: 260–90.
Gemfibrozil	98%	0.14 L/kg	97%	Hepatic/ renal	1.5-2 hr	600 mg PO b.i.d.			Use with caution in patients with CrCl <50 mL/min. Contra-indicated in patients with severe renal dysfunction.	Knopp RH: Drug treatment of lipid disorders. N Engl J Med 1999;341: 498–511.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 26, 27.

Continued

Table A1–1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XIX. Nicotinic Acid										
Niacin	60-76%	ND	ND	Hepatic/renal	45 min	Immediate release: 1-3 g/day in 2-3 divided doses (slow dose titration needed to improve tolerability) Extended release: 500 mg PO q.h.s. initially, increase after 4 wk to 1000 mg PO q.h.s. Max dose = 2000 mg PO q.h.s.	NS	Hyperglycemia, hyperuricemia, GI upset, flushing, tingling, hepatotoxicity, diarrhea, itching, thrombocytopenia (rarely).	Take with food or light snack. Taking aspirin 30 min before niacin may minimize flushing.	
For abbreviations, see p. 864. For further discussion, see Chapter(s) 23.										
XX. Cholesterol Absorption Inhibitor										
Ezetimibe	ND	105 L/kg	> 90%	Intestinal glucuronidation	19-30 hr	10 mg PO q.d	Cyclosporine and fibric acid derivatives increase ezetimibe concentrations. Cholestyramine, colestipol, colesevelam may decrease absorption of ezetimibe.	Diarrhea, myalgia hypersensitivity reactions Myopathy, ↑ creatine kinase and ↑ LFTs (more common when administered with HMG-CoA reductase inhibitor)	Not recommended for use in patients taking gemfibrozil.	Nutescu EA, Shapiro NL. Ezetimibe: A selective cholesterol absorption inhibitor. Pharmacotherapy 2003;23: 1463-74.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXI. Thiazide Diuretics										
Chlorothiazide	30-50%	0.20 ± 0.08 L/kg	ND	Renal	1.5 hr	PO: 125-1000 mg/day in 1-2 divided doses IV: 250-1000 mg/day in 1-2 divided doses	May increase serum lithium concentrations.	Hypokalemia, hypomagnesemia, hypercalcemia, orthostatic hypotension, interstitial nephritis, hyperuricemia, hyperglycemia, photosensitivity reactions.		Sica DA, Gehr T: Diuretics in congestive heart failure. Cardiol Clin 1989;7:87-97; Brater DC: Diuretic therapy. N Engl J Med 1998;339: 387-95.
Chlorthalidone	64%	3-13 L/kg	75%	Renal/hepatic	24-55 hr	12.5-50 mg PO q.d.				
Hydrochloro-thiazide	65-75%	0.83 ± 0.31 L/kg	58 ± 17%	Renal	2.5 hr	12.5-50 mg PO q.d.			Hydrochlorothiazide is contraindicated in patients taking dofetilide.	
Indapamide	93%	24-25 L	~75%	Hepatic/ renal	15-25 hr	1.25-5 mg/day PO q.d.				
Metolazone	40-65%	ND	95%	Renal	8-14 hr, prolonged in CHF and RI	2.5-10 mg/day PO in 1-2 divided doses; maximum dose = 20 mg/ day				

For abbreviations, see p. 864. For further discussion, see Chapter(s) 14, 17, 30.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXII. Aldosterone Antagonists										
Eplerenone	ND	43-90 L	50%	Hepatic CYP3A4	4-6 h	Post-MI LVD: 25 mg PO q.d. titrated to 50 mg/day within 4 wk HTN: 50 mg PO q.d. titrated to 50 mg PO bid	Use contraindicated with potent CYP3A4 inhibitors, such as clarithromycin, erythromycin, ketoconazole, itraconazole, ritonavir, nelfinavir, imatinib, and troleandomycin Eplerenone concentrations may be increased by other CYP3A4 inhibitors including erythromycin, fluconazole, saquinavir, and verapamil	Hyperkalemia, hyponatremia, hypotension, abnormal vaginal bleeding gynecomastia (rare), ↑ LFTs	Avoid if K >5.5 mEq/L or CrCl < 30 mL/min (< 50 mL/min if being used for HTN) Should not be used in patients taking potassium supplements	Keating GM, Plosker GL: Eplerenone: A review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. Drugs 2004;64:2689-707.
Spironolactone	90%	14 ± 4 L/kg	90%	Hepatic	1.5 hr, >15 hr for active metabolites	Cirrhosis: 50-200 mg/day in 1-2 divided doses CHF: 12.5-50 mg PO q.d.	NS	Hyperkalemia, hyponatremia, orthostatic hypotension, gynecomastia, breast tenderness, decreased libido.	Use with caution when SCr > 2.5 mg/dL or K > 5 mEq/L.	Pitt B, Zannad F, Remme WJ, et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341: 709-17.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 11, 14.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXIII. α_1-Antagonists										
Doxazosin	63 ± 14%	1.5 ± 0.3 L/kg	99%	Hepatic	8-12 hr	1-16 mg/day in 1-2 divided doses	NS	First-dose syncope, orthostatic hypotension, dizziness, headache, urinary frequency, priapism (rarely). Phentolamine: hypotension, angina, tachycardia, flushing, headache. Concomitant use of sildenafil, tadalafil, or vardenofil may cause symptomatic hypotension.	Initial dose = 1 mg PO q.h.s. to minimize orthostasis	
Phentolamine	N/A	ND	ND	Hepatic	19 min	Hypertensive emergency: 2-5 mg IV q 5-10 min prn	NS		Both an α_1- and α_2-antagonist	
Prazosin	68 ± 17%	0.63 ± 0.14 L/kg	95%	Hepatic	2-3 hr	1-20 mg/day in 2-3 divided doses	NS		Initial dose = 1 mg PO q.h.s. to minimize orthostasis	
Terazosin	90%	0.8 ± 0.18 L/kg	90-94%	Hepatic/renal	14-16 hr	1-20 mg/day in 1-2 divided doses	NS		Initial dose = 1 mg PO q.h.s. to minimize orthostasis	

Doxazosin arm of the ALLHAT Study terminated early after interim analysis demonstrated increased risk of stroke and CHF in the doxazosin arm when compared with chlorthalidone therapy. References for α_1-antagonists section: Fulton B, Wagstaff AJ, Sorkin EM: Doxazosin. An update of its clinical pharmacology and therapeutic applications in hypertension and benign prostatic hyperplasia. Drugs 1995;49:295-320; Vincet J, Meredity PA, Reid JL, et al: Clinical pharmacokinetics of prazosin—1985. Clin Pharmacokinet 1985;10:144-54; Titmarsh S, Monk JP: Terazosin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. Drugs 1987;33:461-77; The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlorthalidone. The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). JAMA 2000;283:1967-75.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 14, 30.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXIV. Central α_2-Receptor Agonists										
Clonidine	75-95%	2.1 ± 0.4 L/kg	20%	Hepatic/ renal	12 ± 7 hr	PO: 0.1-1.2 mg/day in 2 divided doses Patch: Initially 0.1 mg/24 hr patch applied every wk Dose may be increased after 1-2 weeks by 0.1 mg/ 24 hr to a max of 0.6 mg/ 24 hr	NS	Sedation, drowsiness, dry mouth, bradycardia, conduction abnormalities, orthostatic hypotension. Do not stop abruptly because of the possibility of rebound hypertension. Maximum serum concentrations are reached in 2-3 days after starting therapy with patch; therefore overlapping oral therapy may be necessary.		Lowenthal DT, Matzek KM, MacGregor TR: Clinical pharmacokinetics of clonidine. Clin Pharmacokinet 1988;14: 287-310.

Methyldopa	42 ± 16%	0.46 ± 0.15 L/kg	10-15%	Renal/ hepatic	1.8 ± 0.6 hr	500-2000 mg/day PO in 2-3 divided doses	NS	Sedation, drowsiness, dry mouth, bradycardia, conduction abnormalities, headache, orthostatic hypotension, sodium and water retention (concurrent diuretic therapy is often necessary), positive Coombs test (10-20%), hemolytic anemia (<1%), ↑ LFTs, lupus-like syndrome, blood dyscrasias.		Myhre E, Rugstad HE, Hansen T: Clinical pharmacokinetics of methyldopa. Clin Pharmacokinet 1982;7: 221-33.

For abbreviations, see p. 864. For further discussion, see Chapter 30.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXV. Miscellaneous Antihypertensive Agents										
Fenoldopam	N/A	↑ nonlinearly with dosage; (0.23-0.67 L/kg)	88%	Hepatic	5-10 min	Initial dose of 0.1 μg/kg/min IV continuous infusion titrated by 0.05-0.1 mcg/kg/min no more frequently than every 15 min. Max dose = 1.6 mcg/kg/min.	NS	Headache, tachycardia, nausea, flushing; use with caution in patients with glaucoma.		Oparil S, Aronson S, Deeb GM, et al: Fenoldopam: A new parenteral antihypertensive. Am J Hypertens 1999;12:653-64
Reserpine	40%	ND	96%	Hepatic	5-100 hr	0.05-0.25 mg PO q.d.	NS	Sedation, dizziness, depression (dose-related effect), sodium and water retention (concomitant diuretic therapy may be necessary), diarrhea, dry mouth, peripheral edema, bradycardia, conduction abnormalities.		

For abbreviations, see p. 864. For further discussion, see Chapter 30.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXVI. Vasodilators										
Diazoxide	91%	0.21 L/kg	94%	Hepatic/renal	48 hr (duration of anti-hypertensive effect <12 hr)	Hypertensive emergency: 50-150 mg IV bolus q 5-15 min until desired BP achieved or 15 mg/min by continuous IV infusion for 20-30 min	NS	Tachycardia, fluid retention, angina, nausea, hyperglycemia.		Kirsten R, Nelson K, Kirsten D, et al: Clinical pharmacokinetics of vasodilators: Part 1. Clin Pharmacokinet 1998;34:457-82. Kirsten R, Nelson K, Kirsten D, et al: Clinical pharmacokinetics of vasodilators: Part 2. Clin Pharmacokinet 1998;35:9-36.
Hydralazine	16 ± 6% (rapid acetylator) 35 ± 4% (slow acetylator)	1.5 L/kg	88%	Hepatic	0.96 ± 0.28 hr	HTN(PO): 40-300 mg/day in 3-4 divided doses HTN(IV): 10-20 mg IV prn q 2-4 hr (administer at rate no faster than 10 mg over 1 min) CHF: (given in combination with isosorbide dinitrate) 10-25 mg PO t.i.d. to start titrated to a target dose of 75 mg PO t.i.d.	NS	Headache, palpitations, reflex tachycardia, fluid retention, angina, edema, lupus-like syndrome.		
Minoxidil	95%	2.7 L/kg	0%	Hepatic	3.5-4.2 hr	2.5-40 mg/day in 1-2 divided doses	Do not administer concomitantly with guanethidine; guanethidine must be discontinued for 1-3 wk before initiating therapy with minoxidil.	Profound vasodilation results in reflex tachycardia, sodium and water retention, hypertrichosis, rash.		

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXVI. Vasodilators—cont'd										
Nesiritide	N/A	0.19 L/kg	ND	Proteolysis	18-23 min	CHF: 2 mcg/kg IV bolus followed by 0.01 mcg/kg/min. May increase by 0.005 mcg/kg/min no more frequently than every 3 hours to a max of 0.03 mcg/kg/min	ND	Hypotension	Avoid in patients with cardiogenic shock or if SBP < 90 mm Hg	Keating GM, Goa KL: Nesiritide: A review of its use in acute decompensated heart failure. Drugs 2003;63:47-70
Nitroprusside	N/A	ND	ND	RBCs/tissue	2 min (nitroprusside), 3-4 days (thiocyanate); prolonged in RI	IV: 0.5 mcg/kg/min CI to start, increase dose every 5-10 min to desired effect. Max dose = 10 mcg/kg/min. IC: 100-200 mcg to treat "no reflow" or "slow flow"	NS	Nausea, headache, palpitations, dizziness, thiocyanate toxicity (fatigue, anorexia, disorientation, hallucinations), cyanide toxicity (dyspnea, vomiting, dizziness, weak pulse, dilated pupils, almond breath, shallow breathing, convulsions), methemoglobinemia.	Maximum dose should not be used for longer than 10 min. Thiocyanate blood levels of 50-100 mcg/mL are usually associated with toxicity.	Kirsten R, Nelson K, Kirsten D, et al: Clinical pharmacokinetics of vasodilators: Part 1. Clin Pharmacokinet 1998;34:457-82. Kirsten R, Nelson K, Kirsten D, et al: Clinical pharmacokinetics of vasodilators: Part 2. Clin Pharmacokinet 1998;35:9-36.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 14, 17, 30, 37.

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXVII. Agents Used in Association with Cardiovascular Procedures										
Diazepam	N/A	1-2 L/kg	98%	Hepatic	20-80 hr (duration after single dose = 30-90 min)	Conscious sedation: 2-10 mg IV (not to exceed 5 mg/min), dose may be repeated q 15-30 min to desired effect of max of 30 mg	NS	Pain or venous irritation at site of injection, respiratory depression, confusion, disorientation.		Kixmiller JM, Schick L: Conscious sedation in cardiovascular procedures. Crit Care Nurs Clin North Am 1997; 9:301-12. Popma JJ, Bittl J: Coronary angiography and intravascular ultrasonography. In Braunwald E, Zipes DP, Libby P (eds): Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed. Philadelphia, WB Saunders, 2001, p 387.
Diphenhydramine	61 ± 25%	4.5 ± 2.8 L/kg	85%	Hepatic	7-11 hr (↑ in elderly patients)	PO: (radiocontrast sensitivity prophylaxis) 50 mg PO × 1; 1 hr prior to procedure	NS	Dry mouth, urinary retention, constipation, confusion, disorientation, sedation.		
Fentanyl	N/A	4 ± 0.4 L/kg	80-85%	Hepatic/ extrahepatic sites	1.5-6 hr (duration after single dose = 30-60 min)	Conscious sedation: 0.5 mcg/kg IV (up to 40 mcg); repeat q 10 min until desired effect	NS	Respiratory depression, nausea, vomiting, constipation, confusion, disorientation.		
Midazolam	N/A	1-3 L/kg	97%	Hepatic (CYP 3A4)	~50 min (duration after single dose = 30-60 min)	Conscious sedation: 1-2 mg IV over 2 min, repeated doses can be given q 2 min to a max of 5 mg	Effect may be increased by drugs that inhibit CYP 3A4	Hypotension (rapid administration), respiratory depression, confusion, disorientation.		
Prednisone	80 ± 11%	0.97 ± 0.11 L/kg	75%	Hepatic	3.5 hr	PO: (radiocontrast sensitivity prophylaxis) 60 mg PO × 1; given 12 hr prior to procedure	NS	Hyperglycemia, euphoria, fluid retention.		

For abbreviations, see p. 864.

Continued

Table A1-1—cont'd

	F	V_d	Protein Binding	Elim	$T_{1/2}$	Dose	PKIN Drug Interactions	Clinical Cautions	Notes	Reference
XXVIII. Vasopressors										
Epinephrine	N/A	ND	ND	Hepatic/tissue	1-2 min	Hemodynamic support: 1-10 mcg/min	Avoid MAO inhibitors	Hypertension, arrhythmias, decreased peripheral perfusion, angina, painful extravasation.		
Norepinephrine	N/A	ND	ND	Hepatic/tissue	2 min	Hemodynamic support: 2-20 mcg/min	Avoid MAO inhibitors	Hypertension, arrhythmias, decreased peripheral perfusion, angina, painful extravasation.		
Phenylephrine	N/A	>40 L	ND	Hepatic/tissue	2-3 hr	Hemodynamic support: 30-300 mcg/min	Avoid MAO inhibitors	Reflex bradycardia, hypertension, painful extravasation.		Hengstmann JH, Goronzy J: Pharmacokinetics of 3H-phenylephrine in man. Eur J Clin Pharmacol 1982;21:335-41.

For abbreviations, see p. 864. For further discussion, see Chapter(s) 11, 17.

Appendix 2

Pacemakers and Implantable Cardioverter-Defibrillators

William H. Maisel

Pacemaker (PM) and implantable cardioverter-defibrillator (ICD) systems consist of a pulse generator and electrodes (leads). Devices may be single chamber, dual chamber, or biventricular. Chest roentgenogram appearance of typical PM and ICD systems is shown in Figure A2–1.

PART A—PACEMAKERS

Leads

A variety of pacing leads are commercially available. They vary with respect to fixation mechanism, insulation type, configuration (unipolar versus bipolar), and connector type (Table A2–1). *Lead impedance* may be used as a measure of lead integrity. A low lead impedance may be due to an insulation defect, while high lead impedances may indicate a lead fracture.

Basic Pacing Concepts

Stimulation threshold is the minimum electrical stimulus necessary to consistently capture the heart outside of the heart's refractory period. The threshold can be described by the "strength-duration curve" (Fig. A2–2), which plots amplitude (measured in volts) versus pulse width (measured in msec). Values on or above the curve will result in capture. Pacing at an output below threshold will result in *failure to capture* (Fig. A2–3). This should be distinguished from *no output* conditions (such as those due to a depleted pulse generator battery), where no pacing artifact is present.

Sensing is the ability of the pacemaker to detect the heart's intrinsic rhythm. *Intrinsic amplitude* refers to the size (measured in millivolts) of the detected electrical signal from the atrium or ventricle. *Sensitivity* is a programmable setting above which electrical signals will be interpreted as cardiac in origin and below which electrical signals will be ignored (Fig. A2–4). *Undersensing* is the failure of the pacemaker to detect the intrinsic cardiac electrical signal (see Fig. A2–4). *Oversensing* is the sensing of an inappropriate signal (either physiologic or nonphysiologic) (see Fig. A2–4). Table A2–2 lists some potential sources of electromagnetic interference that can cause oversensing. A magnet, when placed over a pacemaker, disables the pacemaker's ability to sense, resulting in continuous "asynchronous" pacing.

Pacemaker Programming Considerations

Mode—The programmable pacing mode determines in which chambers the pacemaker paces and senses and how it responds to sensed signals (Table A2–3).[1] Examples of the potential ECG appearance of proper dual chamber pacing are shown in Figure A2–5.

Rate Responsive Pacing—This is designed to result in an increase in heart rate proportional to an increase in metabolic demand. It is typically used for patients with sick sinus syndrome. A variety of sensors are available for detecting increases in metabolic demand (Table A2–4).

Pseudo Pacemaker Malfunction

There are a number of programming features that may result in the appearance of pacemaker malfunction, i.e. the pacemaker failing to pace at the programmed rate (Table A2–5).

PART B—IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Like pacemakers, ICDs can be single chamber, dual chamber, or biventricular (see Fig. A2–1). An ICD system can be distinguished from a pacemaker system by the presence of one or two shocking coils (see Fig. A2–1). ICD generators consist of a battery, a capacitor, circuitry, and the device housing or "can."

Programmed Therapies for Ventricular Arrhythmias

ICDs continuously monitor the patient's heart rate. When prespecified, programmable detection criteria are met, the device delivers therapy to restore the patient's rhythm back to normal. Therapies are programmed according to heart rate or "zones." Each zone is programmable and specifies the heart rate range and duration of arrhythmia required before declaring an arrhythmia present and initiating delivery of therapy (Table A2–6).

ICDs can deliver two types of therapies to terminate ventricular arrhythmias: high-voltage therapies (i.e., shocks) or anti-tachycardia pacing (ATP). High-voltage shocks (typically 30 to 40 J maximum) are usually delivered from the ICD and SVC coil to the RV coil, although alternate shocking configurations may be used (Fig. A2–6). Modern devices deliver biphasic shocks (energy flow reverses direction during delivery), which are more energy efficient than older devices that delivered monophasic shocks. Some devices also allow for programming of the tilt (the drop in voltage during discharge), with 50% and 65% being the values most commonly used. ATP may be used to painlessly terminate ventricular

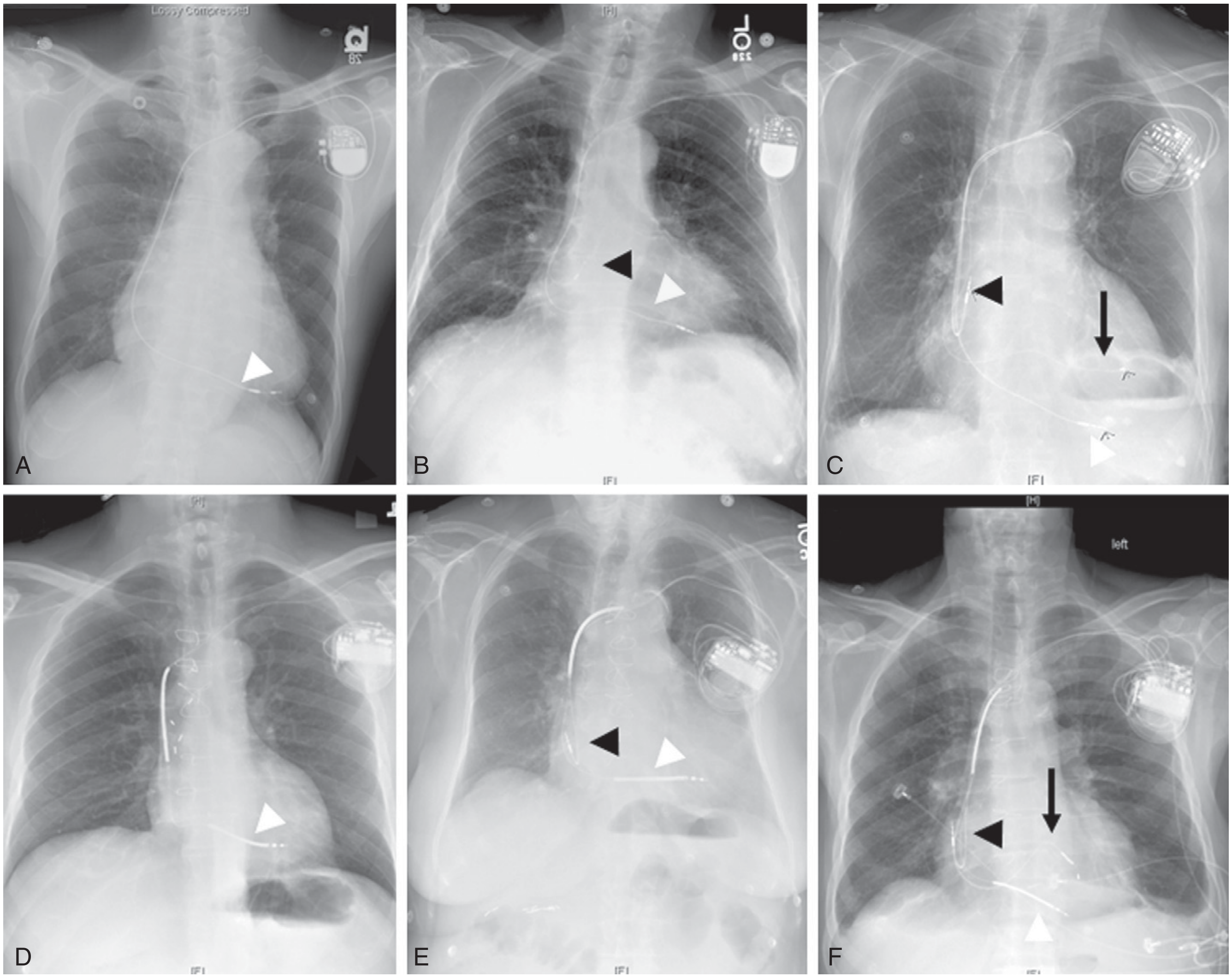

Figure A2–1 Chest roentgenogram appearance of standard pacemaker and implantable cardioverter-defibrillator (ICD) systems is shown. **A,** Single-chamber pacemaker; **B,** Dual-chamber pacemaker; **C,** Biventricular pacemaker; **D,** Single-chamber ICD; **E,** Dual-chamber ICD; **F,** Biventricular ICD. Single-chamber systems consist of a right ventricular (RV) electrode *(white arrowhead).* Dual chamber systems have a right atrial *(black arrowhead)* and RV electrode, while biventricular systems have a third lead positioned in the coronary sinus *(black arrow).*

tachycardia, typically by delivering 6 to 10 paced beats at a rate slightly faster than the tachycardia. ATP is successful at terminating even rapid VT up to 80% of the time.[2] A typical example of ICD programmed zones and therapies is displayed in Table A2–5.

The defibrillation threshold (DFT) or upper limit of vulnerability is tested in each ICD patient at implant and at intervals thereafter.[3] This value is the amount of energy required to terminate ventricular fibrillation and restore sinus rhythm. The maximum device output should be 7 to 10 J above the DFT or ULV to allow reliable defibrillation under clinical conditions.[4] A number of medications can affect the DFT, most notably antiarrhythmia drugs (Table A2–7).[5]

Magnet Operation

All modern ICDs are also pacemakers and, as such, they have the ability to treat not only rapid heart rhythms but slow ones as well. ICDs differ from pacemakers, however, in their response to magnet application. Although pacemakers revert to asynchronous pacing in the presence of a magnet, ICDs do not. For most ICDs, magnets deactivate tachyarrhythmia detection (sensing) while the magnet is directly over the device. Removal of the magnet restores device function to normal.

"Inappropriate Shocks"

An inappropriate shock is the delivery of a shock to the patient for a reason other than a sustained ventricular arrhythmia. Rapid heart rates of nonventricular origin (sinus tachycardia or atrial fibrillation with a rapid ventricular response rate) resulting in ICD shocks occur in 12% of ICD patients.[6] Environmental noise or "noise" due to a lead abnormality (insulation breech or lead fracture) may also lead to inappropriate shocks.

Table A2–1 Pacing Electrode Features

Type	Comment
Fixation Mechanism	
Transvenous, passive fixation	Tines become lodged in trabeculations. Lower pacing threshold, higher dislodgement rate.
Transvenous, active fixation	Helix or screw extends into endocardial tissue to secure lead. Higher pacing thresholds, lower dislodgement rate.
Epicardial	Surgically implanted on outer surface of heart. Typically higher pacing thresholds. May be used for patients with mechanical tricuspid valve, those with difficult coronary sinus access requiring LV pacing, or those requiring PM undergoing concurrent cardiac surgery.
Insulation	
Polyurethane	Easier to pass, more rigid, less durable, thinner.
Silicone	Higher coefficient of friction, therefore less "slippery," less rigid, more durable, thicker.
Configuration	
Unipolar	Sensing and pacing between the lead tip (distal electrode) and the pacemaker pulse generator. Bigger "antenna," therefore more prone to oversensing.
Bipolar	Sensing and pacing between two electrodes separated by several millimeters (proximal and distal) located on a single lead. Smaller "antenna," therefore less prone to oversensing.
Connector Type	
IS-1 bipolar, IS-1 unipolar, 3.2 mm C, 3.2 mm LP, 4.75 mm, 4.75 mm bifurcated, 5 mm UNI, 5 mm, 5 mm bifurcated, 5/6 mm UNI, 6 mm bifurcated, 6 mm linear bipolar, 6.1 mm, 6.5 mm, VS-1, VS-1A, VS-1B	Lead connector and generator header must be compatible. IS-1 is most common connector in use today.

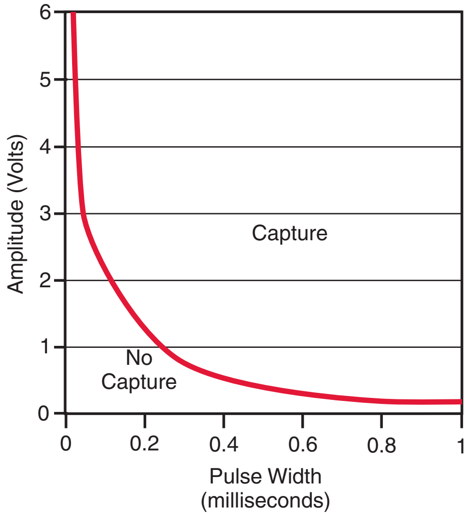

Figure A2–2 A strength-duration curve is shown. It describes the relationship between the amplitude (in volts) and the pulse width (in milliseconds). Values on or above the curve result in capture. Values below the curve will result in failure to capture.

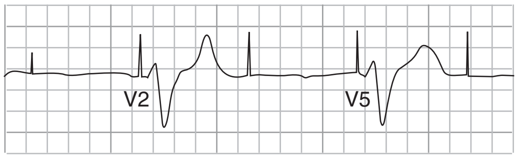

Figure A2–3 An example of intermittent failure to capture is shown. Pacing spikes can be seen marching steadily through the tracing, but every other beat fails to elicit ventricular depolarization. This can occur due to elevated pacing thresholds, a low programmed pacemaker output, a depleted pulse generator battery, lead abnormality, or a prolonged refractory period.

Table A2–2 Potential Sources of Electromagnetic Interference

Electrocautery
Transthoracic defibrillation
Lithotripsy
Therapeutic radiation
Radiofrequency ablation
MRI
Cellular telephones
Airport security
Anti-theft devices
Magnets

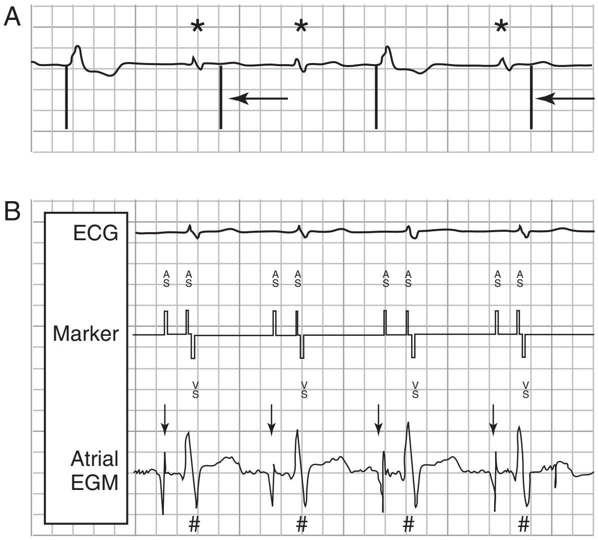

Figure A2–4 **A,** Undersensing of the QRS complex is demonstrated. The first and fourth QRS complexes are ventricular-paced beats. Native QRS complexes (*), however, are not appropriately sensed, resulting in a failure to inhibit pacing. As a result, inappropriate ventricular pacing spikes are present (←). Because they occur in the ventricular refractory period, they result in failure to capture. Reprogramming the pacemaker to a more sensitive setting overcame this problem. The pacing threshold was not elevated. **B,** Atrial oversensing is present. The atrial electrogram (EGM) *(bottom)* obtained during routine pacemaker interrogation demonstrates sensing of the intrinsic atrial signal (↓) and "far-field" oversensing of the ventricular signal (#). This is confirmed by the marker channel (AS = atrial sensed event, VS = ventricular sensed event).

Table A2–3 The Revised NASPE/BPEG Generic Code for Antibradycardia, Adaptive-rate, and Multisite Pacing

Position Category	I Chamber Paced	II Chamber Sensed	III Response to Sensing	IV Rate Modulation	V Multisite Pacing
	0 = None A = Atrium V = Ventricle D = Dual (A + V) S = Single (A or V)	0 = None A = Atrium V = Ventricle D = Dual (A + V) S = Single (A or V)	0 = None T = Triggered I = Inhibited D = Dual (T + I)	0 = None R = Rate Modulation	0 = None A = Atrium V = Ventricle D = Dual (A + V)

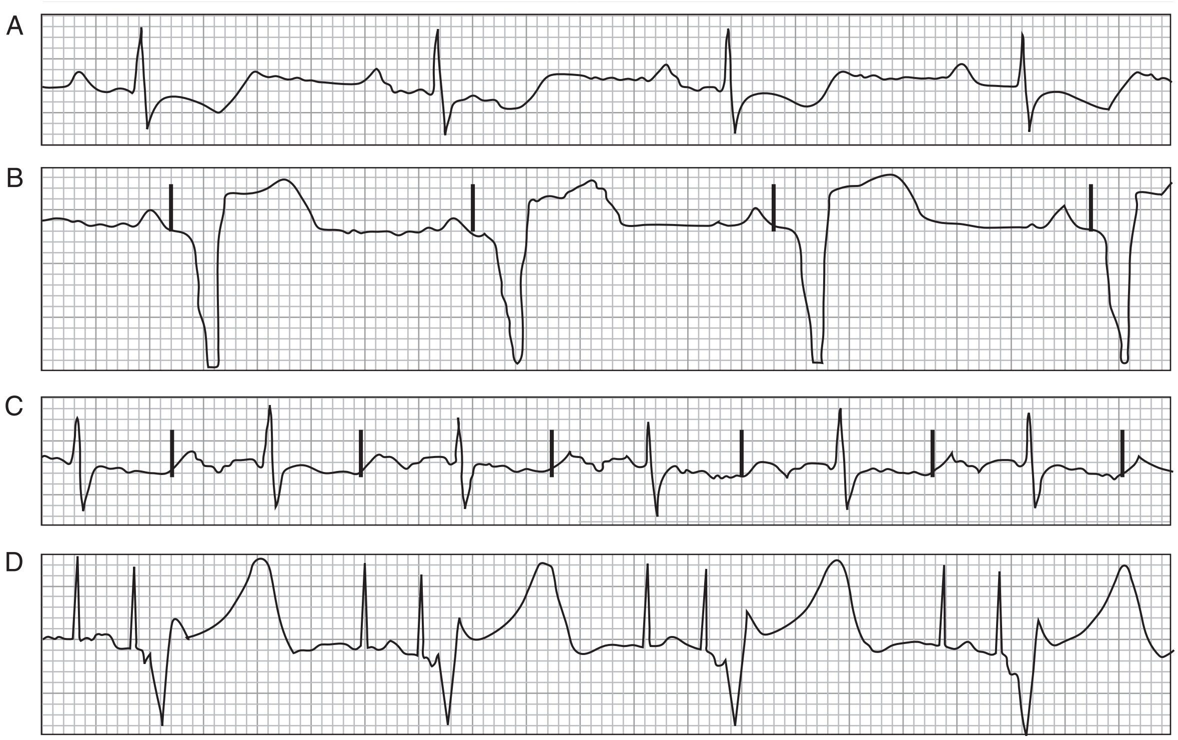

Figure A2–5 Examples of the potential ECG appearance of proper dual-chamber pacing are shown. **A,** Sinus rhythm without pacing. **B,** Sinus rhythm with ventricular pacing. **C,** Atrial pacing with intact atrioventricular conduction. **D,** Dual-chamber pacing.

Table A2–4 Sensors for Rate Responsive Pacing

Type of Sensor	Description	Comments
Motion/activity sensor	**Detects physical movement and increases rate according to level of activity.**	**Brisk response to exercise but does not respond well to other physiologic stresses, such as emotional stress.**
Examples:		
Piezoelectric crystal	Mechanical force causes change in crystal structure that generates voltage.	Can be activated by nonphysiologic stimuli (e.g., vibration while riding in a car).
Accelerometer	Converts change in velocity in anterior-posterior (AP) direction into electrical signal.	May not provide adequate response to activities without movement in AP direction (e.g., weight lifting).
Minute ventilation	**Measures changes in electrical impedance across chest as surrogate marker for respiratory rate.**	**Good correlation with metabolic workload. Does not respond as quickly as motion/activity sensors to onset of exercise.**
Physiologic Sensors	**Assessment of true physiologic measure.**	**Rarely stand-alone sensor for rate responsive pacing. Accuracy varies.**
Examples:		
QT duration	Measured from onset of QRS to end of the T wave	Interval affected by autonomic tone and heart rate. Good rate-adaptive measure. Does not respond well to non–exercise-related stress.
Others:		
pH body temperature force of ventricular contraction	Variety of physiologic measures may correlate with activity	May be part of multisensor PMs in future. Not accurate enough for stand-alone, rate-responsive sensor function.

Table A2–5 Causes of Pseudo-Pacemaker Malfunction

Feature	Description
Mode switch	Device switches from tracking mode (such as DDD) to non–tracking mode (such as DDI) in response to sustained atrial arrhythmia. Mode switch pacing rate may be separately programmable or may be lower rate limit of the pacemaker.
Hysteresis	Allows the rate to fall below the programmed lower rate of the pacemaker following an intrinsic beat.
Rate drop response	Delivers pacing at a programmed high rate (e.g., 100 beats/min) for a limited time in response to a drop in heart rate. Used for patients with neurocardiogenic syncope.
Rate responsive pacing	Increases heart rate in response to activity.
Sleep mode	Allows programming of different lower rate for bedtime hours to minimize pacing and conserve the battery.

DDD, DDI—See Table A2–3 for description of pacing modes.

Most ICDs have programmable features that may reduce the chances of a patient receiving an inappropriate shock (Table A2–8).

Routine Follow-Up

ICD patients require routine outpatient follow-up every 3 to 6 months. At each visit, device interrogation is performed to determine if any significant arrhythmias have occurred in the interval since the patient was last seen. Other parameters that are also routinely checked are battery voltage; full energy charge time (6 to 10 seconds in a new device, 12 to 18 seconds in a device near elective replacement); pacing threshold; intrinsic amplitude; and lead impedance.

Table A2–6 Typical Implantable Cardioverter-Defibrillator Programming

	VT Zone	VF Zone
Heart rate	170-200 beats/min	>200 beats/min
Cycle length	300-350 msec	<300 msec
Detection duration	16 intervals	2 sec
Therapy 1	Burst pacing	24 J
Therapy 2	24 J	35 J
Therapy 3	35 J	35 J
Therapy 4	35 J	35 J
Therapy 5	35 J	35 J

VF, ventricular fibrillation; VT, ventricular tachycardia.
An example of typical ICD programming for tachyarrhythmia detection and treatment is shown. The VT zone is programmed to respond to arrhythmias in the 170 to 200 beat/min range (cycle length 300 to 350 msec). In this case, if 16 intervals are within the programmed VT range, then the device will begin to deliver therapy. Anti-tachycardia pacing (ATP) will be attempted first. If the arrhythmia persists, a series of shocks will be delivered, with the device automatically withholding additional therapy if the rhythm falls below the rate cutoff. If the heart rate is greater than 200 beats/min for 2 sec, then the VF therapies will apply. The first programmed shock is typically 10 J above the defibrillation threshold, with the remainder of the therapies programmed to maximum output.

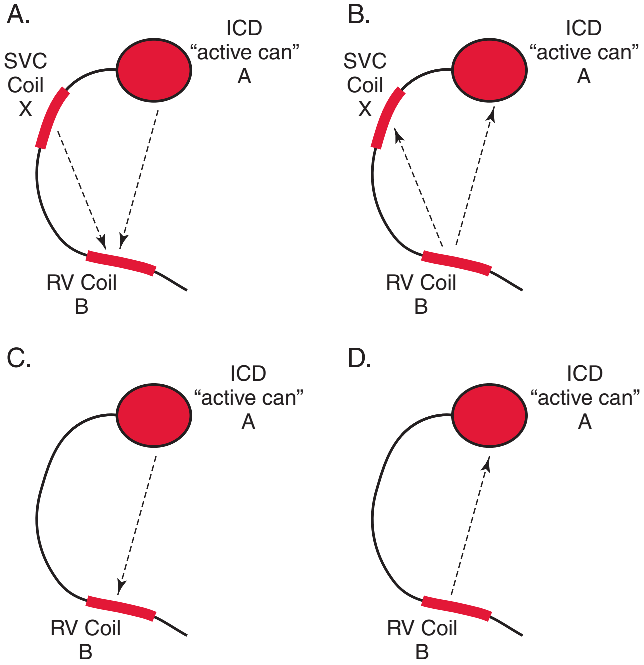

Figure A2–6 A variety of shocking circuit configurations are shown. Transvenous ICD leads may be dual coil (6A and 6B) or single coil (6C and 6D). For dual coil leads, energy is delivered from (A) the ICD ("active can") and SVC coil to the RV coil ("initial" polarity or "AX to B") or (B) from the RV coil to the SVC coil and ICD ("reversed" polarity or "B to AX"). For single-coil leads, energy delivery is from the (C) ICD to the RV coil ("initial" polarity or "A to B") or (D) RV coil to ICD ("reversed" polarity or "B to A"). Dual coil systems have DFTs 5-7 J lower, on average, than single-coil systems. Mean DFT is approximately equal with standard or reversed polarity, although DFT can vary by 5-7 J with different polarity in individual patients. Occasionally, an epicardial system may be encountered, in which energy delivery is between two surgically placed epicardial patches or between an epicardial patch and active can (not shown).

Table A2–7 Medications that can Affect the Defibrillation Threshold

Medication	Effect on DFT
Amiodarone	Increase
Bretylium	Varies
Disopyramide	Increase
Flecainide	Increase
Lidocaine	Increase
Mexiletine	Increase
NAPA	Decrease
Procainamide	Varies
Propafenone	Varies
Sotalol	Decrease
Verapamil	Increase

DFT, defibrillation threshold.

Table A2–8 Arrhythmia Discriminators

Discriminator	How It Works	Clinical Implications
Stability	Measures beat-to-beat variation in arrhythmia cycle length. Withholds therapy for irregular rhythms.	Effective at discriminating between ventricular tachycardia (usually very regular) and rapid atrial fibrillation (usually irregular).
Onset	Measures how sudden the arrhythmia onset was. Withholds therapy unless the arrhythmia begins suddenly.	Effective at discriminating sinus tachycardia from ventricular tachycardia. Ventricular tachycardia is usually sudden in onset, while the heart rate increases more gradually for patients with sinus tachycardia.
Morphology	Compares the QRS configuration during arrhythmia to the baseline QRS configuration. Withholds therapy if the arrhythmia QRS is similar to the baseline QRS.	Can help avoid inappropriate shocks for supraventricular arrhythmias.

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Circulatory Support Devices

James C. Fang and Gregory S. Couper

A wide variety of mechanical cardiac support devices are commercially available in the United States (Table A3–1).[1] They cover a spectrum of effectiveness (hemodynamic power) and invasiveness. Generally, the more completely a device replaces native cardiac function, the more invasive and potentially complicated the implantation procedure becomes. Historically, the purpose of such devices was to provide days to weeks of circulatory support, but today their use has been extended to provide months to years of circulatory support to "bridge" patients to transplantation or myocardial recovery. For patients who are not appropriate for transplantation, a left ventricular assist device (LVAD, HeartMate I XVE) is now also approved for permanent circulatory support.

The least powerful mechanical cardiac assist device is the intra-aortic balloon pump (IABP). The most effective application of the IABP is in ischemic heart failure. Through a combination of diastolic augmentation of coronary blood flow and systolic unloading of the left ventricle, the cardiac output may be supplemented by 15% to 20%. The IABP is also the least invasive device because it can be routinely inserted percutaneously, occasionally without fluoroscopic guidance. Greater hemodynamic support can be achieved with percutaneous cardiopulmonary bypass systems (Bard CPS ReAct System, CR Bard, Billerica, Mass). Their use is primarily limited to the cardiac catheterization laboratory for temporary hemodynamic support during high-risk coronary interventions. Notably, they are also limited by an inability to unload the left ventricle completely and therefore can be used only as short-term support until percutaneous or surgical revascularization can be accomplished. The Tandem Heart PTVA (CardiacAssist, Pittsburgh, Pa) can also be placed percutaneously and provides up to 4 L/min of blood flow using an extracorporeal centrifugal pump. It can provide left ventricular unloading because the inflow cannula sits in the left atrium across the interatrial septum via a transseptal puncture. However, large-bore percutaneous catheters (15 to 17 Fr) are required to provide adequate flow rates into the femoral artery.[2] Ventricular assist devices (VADs) and total artificial hearts (TAHs) can supply 100% of cardiac output under most circumstances. In some conditions the output of VADs can be supplemented by output of the native ventricles. Because the TAH requires removal of the native ventricles, there is no native cardiac function, which is problematic in the event of device failure. In contrast, VADs can ultimately be "backed up" by native ventricular function. In general, implantation of a VAD or TAH requires full open-heart surgery approaches including additional surgical exposure in the abdomen for various components. Newer VADs, such as axial flow pumps, are smaller and can be implanted through a thoracotomy, even while off cardiopulmonary bypass. Most currently available devices have percutaneous catheters or leads. Future devices will be fully implantable with transcutaneous electromagnetic energy transmission providing power or monitoring for internal electrical motors, or both.

PHYSIOLOGY OF MECHANICAL CARDIAC SUPPORT

Intra-Aortic Balloon Pump Counterpulsation

As a mechanical cardiac assist device, the IABP is capable of augmenting cardiac output by a modest degree (generally ≤ 25%). Optimal counterpulsation produces several favorable physiologic effects. Balloon inflation creates an augmented diastolic blood pressure and increase in coronary perfusion pressure. Deflation during the isovolumic phase of systole results in early left ventricular systolic unloading and increases stroke volume. Figure A3–1 depicts a typical arterial tracing during alternate beat support (1:2 timing) with appropriate timing of balloon inflation and deflation. Stroke volume rises because of a decrease in left ventricular afterload resulting from IABP counterpulsation. The isovolumic phase of systole is shortened, and forward ejection occurs earlier. In some decompensated patients, this is sufficient to reestablish an adequate cardiac output, especially if there is an ischemic component to their cardiac failure. Given mixed populations of patients, it has been difficult to ascertain whether left ventricular systolic unloading or aortic diastolic augmentation is the dominant physiologic effect. Right ventricular systolic unloading has also been accomplished with IABP counterpulsation in the pulmonary artery when catastrophic right ventricular failure occurs during cardiac surgery.

Current consoles allow automatic triggering of the balloon pump by native QRS signals, pacing spikes, or pulse pressure detection. Improvements in console and catheter designs have enabled more rapid shuttling of the helium gas in and out of the balloon. As a consequence, there has been improved ability to provide effective counterpulsation despite irregular or rapid rhythms, although there are limits to this ability in individual patients. Usually, an IABP catheter is inserted through an 8 Fr delivery sheath, although smaller arterial access can be achieved if an insertion sheath is not used.

Ventricular Assist Devices and Total Artificial Heart

VADs are powerful pumps and, depending on the specific pump design, can provide most or all of the normal cardiac output under many physiologic conditions. VADs are connected to the left or right heart structures (atria or ventricles and to the corresponding great artery) diverting the blood away from the supported side, essentially bypassing it.

Table A3–1 Representative Examples of Mechanical Assist Devices*

Device	Flow Pattern	BiVAD	Usual Duration of Support	Anticoagulation	Ambulatory	Out-of-Hospital Use	Relative Advantages	Relative Disadvantages
Percutaneous								
Intra-aortic balloon pump†	Cyclic	No	Day/wk	Heparin/Dextran	No	No	Rapid, minimally invasive insertion, minimally thrombotic	Minor boost in cardiac output. Bedridden status
CardiacAssist Tandem Heart PTVA†	Continuous	No	Day/wk	Heparin	No	No	Provides flow up to 4L/min	Large bore percutaneous catheters, transseptal puncture required
Extracorporeal Pneumatic Pumps								
• Abiomed BVS 5000†	Pulsatile	Yes	Day/wk	Heparin	No	No	Low cost, simple automatic operation of VAD/console	Bleeding; thrombogenicity
• Abiomed AB 5000†	Pulsatile	Yes	Wk/mo	Heparin	Yes	No	Compatible with BVS 5000 system	Bleeding
• Thoratec PVAD†	Pulsatile	Yes	Day/wk/mo	Low-dose heparin Coumadin ± antiplatelet therapy	Yes	Yes	Increased mobility, reasonably low thrombogenicity	Relatively large portable console
• Centrifugal pumps Biomedicus† Sarns-3M Terumo† St. Jude†	Continuous	Yes	Day/wk	Heparin	No	No	Simple implant	Bleeding; lack of automatic operation, constant monitoring by hospital staff
• ECMO	Continuous	Yes	Day/wk	Heparin	No	No	Full cardiac and pulmonary support	Bleeding; complexity of operation and monitoring. Potential to fail to unload adequately

Continued

Table A3–1 Representative Examples of Mechanical Assist Devices*–cont'd

Device	Flow Pattern	BiVAD	Usual Duration of Support	Anticoagulation	Ambulatory	Out-of-Hospital Use	Relative Advantages	Relative Disadvantages
Intracorporeal Pulsatile Flow Pumps								
WorldHeart Novacor LVAS†	Pulsatile	No	Wk/mo	Coumadin ± antiplatelet therapy	Yes	Yes	Mechanical durability	Thrombogenicity
Thoratec HeartMate XVE LVAS†‡	Pulsatile	No	Wk/mo	Aspirin	Yes	Yes	Thromboresistant, DT approved, pneumatic backup	Infection, motor/inflow valve failure
Thoratec IVAD†	Pulsatile	Possible	Wk/mo	Coumadin	Yes	Yes	Implantable BiVAD console	Relatively large portable
Axial Flow Pumps								
Jarvik 2000	Continuous	No	Mo/yr	Coumadin	Yes	Yes	Durability, size, thoracotomy implant possible	In clinical trials
HeartMate II LVAS	Continuous	No	Mo/yr	Coumadin	Yes	Yes	Durability, size, thoracotomy implant possible	In clinical trials
Micromed DeBakey	Continuous	No	Mo/yr	Coumadin ± antiplatelet therapy	Yes	Yes	Durability, size, thoracotomy implant possible	In clinical trials
Artificial Heart								
CardioWest TAH†	Pulsatile	Yes	Wk/mo	Coumadin ± antiplatelet therapy	Yes	?Yes	Complete cardiac support	Infection; no cardiac reserve, thrombogenicity

*Currently available or commonly used, or both, in the United States. Other devices may be available worldwide. The field of surgical circulatory support is evolving rapidly. Some new devices now in clinical trials are not listed in this table and may become available in the future.
†FDA approved for use as bridge to transplant or circulatory assistance, or both.
‡Only device currently FDA approved for destination therapy.
BiVAD, biventricular assist device; DT, destination therapy; ECMO, extracorporeal membrane oxygenator; LVAS, left ventricular assist system; TAH, total artificial heart; VAD, ventricular assist device.

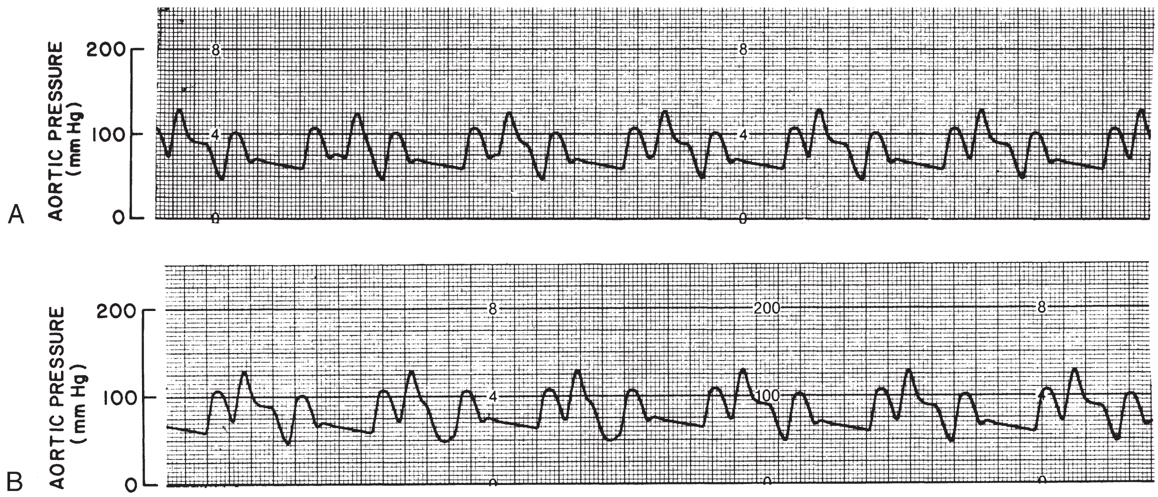

Figure A3–1 **A,** The timing of balloon inflation is adjusted until it occurs late in diastole, uncovering the dicrotic notch. Subsequently, inflation timing is moved earlier in the cardiac cycle until the dicrotic notch on the central aortic tracing just disappears (beat 4). The augmented pressure will rise as inflation timing is moved earlier. **B,** Deflation knob is moved toward the right (later in the cardiac cycle) until the end-diastolic dip is 10 to 15 mm Hg below the patient's unassisted diastolic pressure. This provides a maximal lowering of the patient's unassisted systolic pressure. (From Baim DS, Grossman W [eds]: Cardiac Catheterization, Angiography, and Intervention. Baltimore, Williams & Wilkins, 1996, p 426.)

Cannula length depends on the device, chambers cannulated, and position of the blood pump relative to the heart. The native heart remains to recover or, in the rare event of VAD failure, resume native cardiac output. The TAH completely replaces the function of the removed native ventricles. As a result, failure of the TAH is immediately fatal.

Blood may be pumped using the devices in two basic fashions: (1) pulsatile flow or (2) minimally pulsatile-continuous flow. The pulsatile flow pumps create normal or sinusoidal pulse waves, often indistinguishable from normal arterial pulse contours (Fig. A3–2). They displace blood volume at physiologic rates, requiring a compensatory volume shift (usually of air) into a compliance chamber or externally to prevent generating a vacuum during the cycle. The pump may be driven by an external pneumatic pump (console) or an internal electric motor. The Thoratec HeartMate I XVE (Thoratec, Pleasanton, CA) is configured for backup pneumatic pumping in the event of internal electrical failure. Examples of pneumatic pumps include the Abiomed BVS 5000 (Abiomed Cardiovascular, Inc., Danvers, MA), the Thoratec PVAD (Thoratec Corp., Pleasanton, CA), the Thoratec Pneumatic HeartMate (Thoratec, Berkeley, CA), and the Cardiowest TAH (SynCardia Systems, Tuscon, AZ). Electric pumps include the Thoratec HeartMate I XVE and the Novacor VADs (WorldHeart, Ottawa, Canada).

Continuous flow pumps are based on centrifugal or axial flow designs. Cyclic variations in flow and outlet pressure may occur as a result of native cardiac activity, resulting in low-amplitude pulse pressure. Greater pulsatility may be achieved through the short-term addition of an IABP. Centrifugal blood pumps were among the first to gain popularity as short-term VADs or in extracorporeal membrane oxygenation (ECMO) systems. Blood volumes remain constant and low (relative to pulsatile pumps) within most rotary pumps, resulting in a much smaller size of blood pumps and cannulas. Similarly, axial flow pumps are smaller and allow for internal implantation in smaller patients, such as women and children (body surface area [BSA] < 1.5 m^2). Finally, durability may be greater with axial flow pumps because they can be powered using magnetically driven and levitated impellers. A large number of promising rotary pumps, both axial and centrifugal, are currently in clinical investigational human trials.

IMPORTANT CLINICAL FACTORS IN MECHANICAL CARDIAC ASSIST

Fulminant Ventricular Arrhythmias

Frequent preoperative ventricular tachycardia or occasional ventricular fibrillation may be tolerable and treatable after LVAD implantation. In fact, the arrhythmias may resolve with resting of the left ventricle. The presence of a mechanical VAD may also result in sufficient hemodynamic stability to allow mapping and ablation of ventricular tachycardia. On occasion, ventricular arrhythmias may worsen after device implantation, presumably due to re-entry around the ventricular cannulation site. In general, post-VAD ventricular arrhythmias should be controlled either pharmacologically or by ablation because sustained ventricular arrhythmias compromise optimal VAD flows and can lead to intraventricular thrombus formation.

However, biventricular assist devices (BiVADs) and, depending on the intent, the TAH provide the most reliable and stable forms of support when fulminant or malignant patterns of ventricular arrhythmias are present. ECMO is temporarily acceptable, especially in the circumstance of cardiac arrest. It may be used as a bridge to an alternative device following stabilization for 1 to 2 days. An atrial septostomy may be required to ensure unloading of the left heart and avoidance of pulmonary edema. This strategy is crucial if the left heart is not ejecting at all.

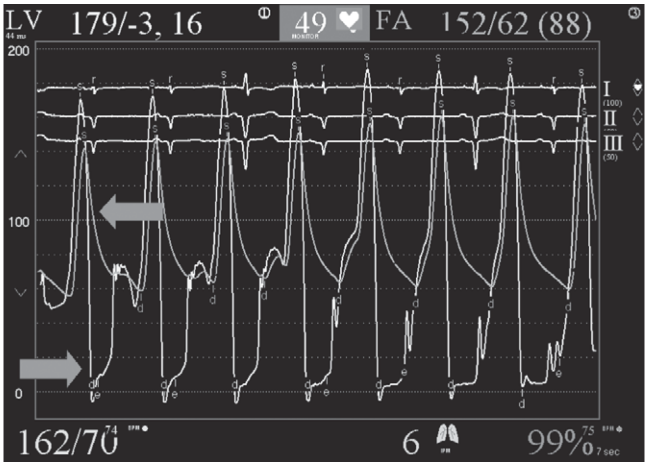

Figure A3–2 (See also Color Plate A3–2.) Simultaneous recording of intraVAD *(right arrow)* and femoral artery pressure *(left arrow)*. Femoral artery waveform similar to native ejection except for increased pulse pressure.

Advanced Hepatic or Renal Dysfunction

Secondary organ dysfunction results from a combination of acute shock, chronic low cardiac output, and passive congestion secondary to right heart failure. When multiple organs exhibit secondary dysfunction, serious consideration should be given to biventricular support rather than isolated left ventricular support. The BiVAD or TAH eliminates problems of right heart failure and marginal cardiac output sometimes seen early after isolated LVAD implantation.

Right Heart Failure

Essentially a clinical diagnosis following isolated LVAD implantation, this problem results in limitation of cardiac output, tricuspid regurgitation, and elevated right atrial pressure with visceral congestion, ascites, and peripheral edema. It is the consequence of interaction between the right ventricle and the afterload (or impedance) of the pulmonary arterial bed. The mismatch of poor right ventricular function (generally defined by a RVEDP or CVP > 20 mm Hg) with normal or low pulmonary arterial pressure and resistance predicts the highest risk for requiring a right ventricular assist device (RVAD) in conjunction with an LVAD.[3] Pharmacologic therapy following isolated LVAD implantation is directed toward inotropic support of the right ventricle and vasodilation (preferentially selective) of the pulmonary arterial tree. With time and chronic unloading of the left ventricle, pulmonary vascular resistance will fall and may allow for weaning of right ventricular inotropic support.

Patient's Size

In patients with a BSA greater than 1.5 m^2, most implantable devices readily fit the thoracic and abdominal cavities. Extremely large patients (BSA > 2.5 m^2) require devices capable of pumping > 6 L/min. Small patients with a BSA < 1.5 m^2 may not be suitable for the implantable pulsatile VADs or TAHs; extracorporeal VADs may be a better option. When BSA is < 1.2 m^2, the Thoratec PVAD may function best because stroke volume can be decreased commensurate with the patient's size. Centrifugal VAD or ECMO is a short-term option in smaller patients, especially in the pediatric population. As reviewed previously, the newer rotary pumps may be implantable over a broader size range than current implantable VADs or TAHs.

Anticoagulation

The use of mechanical devices to support the circulation necessitates the use of anticoagulants, antiplatelet agents, or both to prevent thromboembolic complications. The IABP generally requires systemic anticoagulation with a target activated partial thromboplastin time (aPTT) of 50 to 70 seconds using heparin. For short-term support VADs, such as the Abiomed device, anticoagulation is usually achieved with unfractionated heparin and a target activated clotting time (ACT) of 150 to 200 seconds. Anticoagulation with long-term support VADs, such as the Thoratec device, typically requires warfarin with a target International Normalized Ratio (INR) of 2.0 to 2.5. In contrast, the HeartMate VAD requires only aspirin for anticoagulation because of the formation of a pseudointimal layer in the blood-contacting portion of the titanium housing. However, in all cases of anticoagulation, the therapeutic goals must be individualized to prevent bleeding complications.

Heparin-induced thrombocytopenia (HIT) is an increasingly common management problem in mechanical circulatory support therapy. A number of agents including argatroban, bivalirudin, and fondaparinux have been used by various centers for postoperative care, but there are no current universally accepted strategies. In contrast to heparin, there are no antidotes to the direct antithrombins or anti-Xa agents, a situation that complicates the management of perioperative bleeding and stroke when these drugs are used.

Duration of Support

Bridge to Recovery for Acute Cardiac Failure (Fig. A3–3)

Successful support to recovery following open-heart surgery or myocardial infarction occurs when myocardial stunning is the dominant process. Appropriate selection of patients generally results in use of the device for less than 7 to 10 days. A distinct onset of myocardial dysfunction and acute heart failure characterize fulminant myocarditis. The duration of support required in this setting is highly variable and may last for weeks. Accordingly, a device capable of this duration of support should be chosen. However, the criteria to determine adequacy of myocardial recovery remain unclear and in most cases, myocardial recovery will be uncommon.[4-6]

Bridge to Transplantation (Fig. A3–4)

Numerous patient-related factors affect the length of time that the device is used while waiting for a transplant. A long wait can be anticipated if the patient is of large size or has been highly sensitized to human leukocyte antigens. The position of the patient on a transplant list depends on the current logistics of the regional organ bank (number of patients at the same status and with the same blood type), which can vary over time.

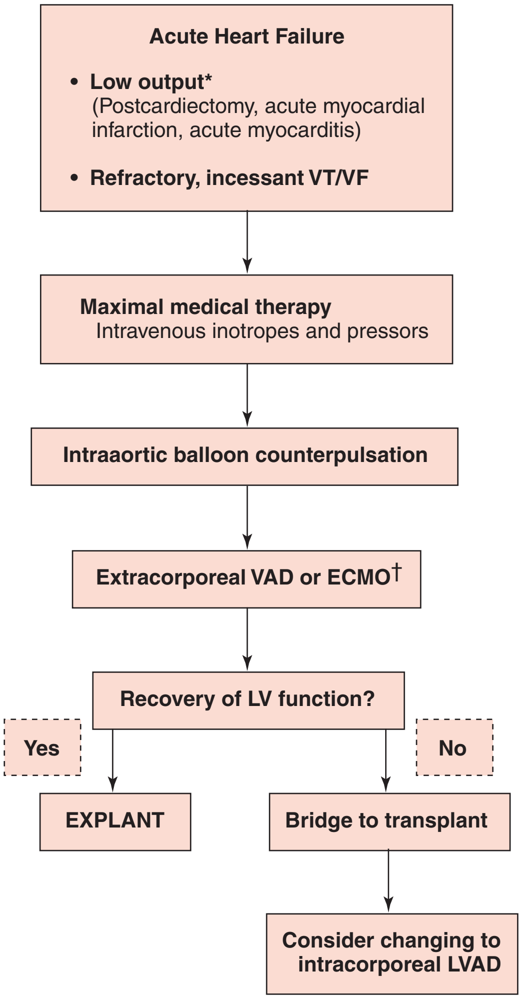

Figure A3–3 Acute heart failure. ECMO, extracorporeal membrane oxygenation; LV, left ventricle; LVAD, left ventricular assist device; VAD, ventricular assist device; VF, ventricular fibrillation; VT, ventricular tachycardia. *Low output may be defined by but not limited to cardiac index < 2 L/min/m^2, systolic blood pressure < 80 mm Hg, wedge pressure > 20. †See Chapter 17 for discussion regarding preoperative factors to consider before VAD placement.

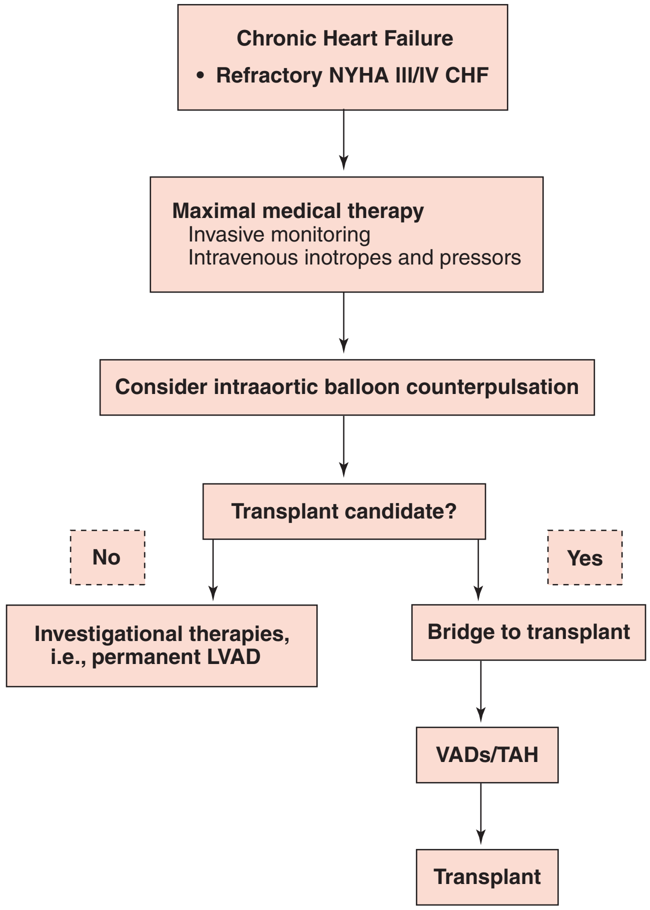

Figure A3–4 Chronic heart failure. LVAD, left ventricular assist device; TAH, total artificial heart; VADs, ventricular assist devices.

Particular patient-related problems require prolonged mechanical support before cardiac transplantation for resolution. Examples include advanced multi-organ dysfunction, severe physical debility, malnutrition with cachexia, and severe pulmonary arterial hypertension.

Possible candidates for transplantation need to meet typical inclusion and exclusion guidelines (see Chapter 17). During prolonged support, implantable LVADs offer the advantage of discharge to home, avoiding further nosocomial complications.

PERMANENT SUPPORT (DESTINATION THERAPY)

The landmark REMATCH trial established the superiority of VAD support over medical management (i.e., intravenous inotropic support) for endstage heart failure in patients deemed not appropriate for cardiac transplantation.[7] The Centers for Medicare and Medicaid Reimbursement and the FDA have established guidelines for selection of patients. These criteria include the presence of medically refractory New York Heart Association class IV heart failure, the determination that the patient is not a transplant candidate, and the patient's life expectancy of less than 2 years. However, it should be noted that device failure is a major limitation with this strategy and often occurs within 18 months of implantation. Replacement of the VAD or its dysfunctional parts (i.e., inflow valve regurgitation) can be performed but is fraught with the usual problems associated with major recurrent cardiovascular surgery (see later). Currently, only the Thoratec HeartMate XVE LVAS is approved in the United States for destination therapy.

Conversion of Devices

When the intent of support shifts from an initial short-term bridge to recovery to longer duration support, conversion from a short-term support device, such as a centrifugal VAD, ECMO, or an extracorporeal VAD (i.e., Abiomed), to a device with long-term support capability may be necessary. In the absence of ongoing severe ventricular arrhythmias, hepatic

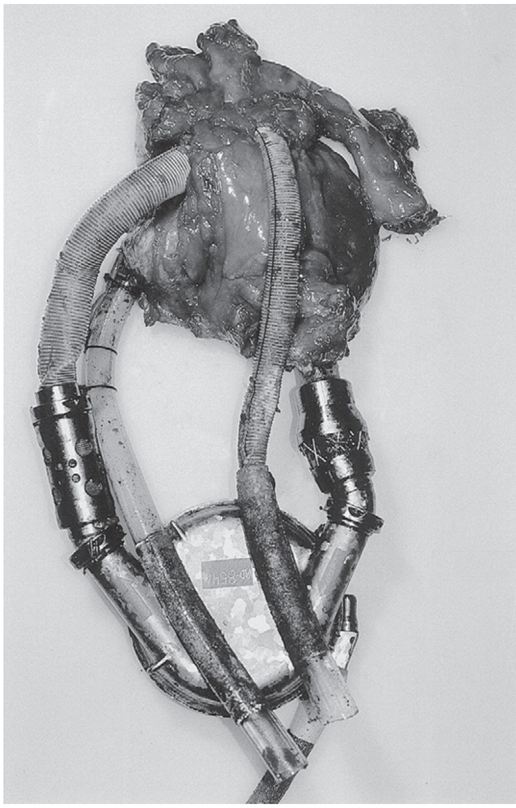

Figure A3–5 (See also Color Plate A3–5.) Explanted heart demonstrating use of two different ventricular assist devices for "hybrid" biventricular support, involving both intracorporeal and extracorporeal systems. Left ventricular assist device is the Thoratec HeartMate with inflow cannula in the left ventricular apex and outflow cannula (Dacron tubing on left of photograph) in the ascending aorta. Right ventricular assist device is the Thoratec (extracorporeal device not shown) with inflow cannula in right atrium and outflow cannula (Dacron tubing in middle of photograph) in main pulmonary artery. (Courtesy Marc Barry, MD, and Greg Couper, MD, Brigham and Women's Hospital, Boston.)

and renal insufficiency, or right ventricular failure, conversion to an isolated LVAD is likely to be successful. When the clinical situation requires prolonged biventricular assist, devices such as the Thoratec VAD or TAH are the best solution, avoiding hybrid systems (Fig. A3–5) that typically result in lower success rates.

DEVICE DYSFUNCTION AND INFECTION

Device failure is an inevitable complication of currently approved device technology, attributable to the "wear and tear" introduced to mechanical systems that face variable stresses and strains. In contrast, the newer continuous flow pumps may obviate this issue due to the electromagnetic system that drives the impellers. The most common device malfunctions involve either degeneration of the inflow valve leading to VAD "regurgitation" and bearing wear in the motor that leads to pump failure. Recent modifications to VAD design and software have improved the longevity of these devices. Diagnosis of the presence of such mechanical problems can generally be made by waveform analysis, exit filter analysis, device fluoroscopy, echocardiography,[8] and cardiac catheterization.[9] Infections generally involve the percutaneous driveline and can be managed by careful surgical wound care and antibiotic therapy. Unresponsive infections require surgical creation of a new percutaneous driveline track or even device explantation.

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